EPA
United States
Environmental Protection
Agency

MINISTRY OF ENVIRONMENTAL PROTECTION
THE PEOPLE'S REPUBLIC OF CHINA

Environmental Health Risk Assessment in the United States: Methods and Experiences

An overview of Environmental Human Health Risk Assessment at the U.S. EPA

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Environmental Health Training Program
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Office of Research and Development
National Center for Environmental Assessment

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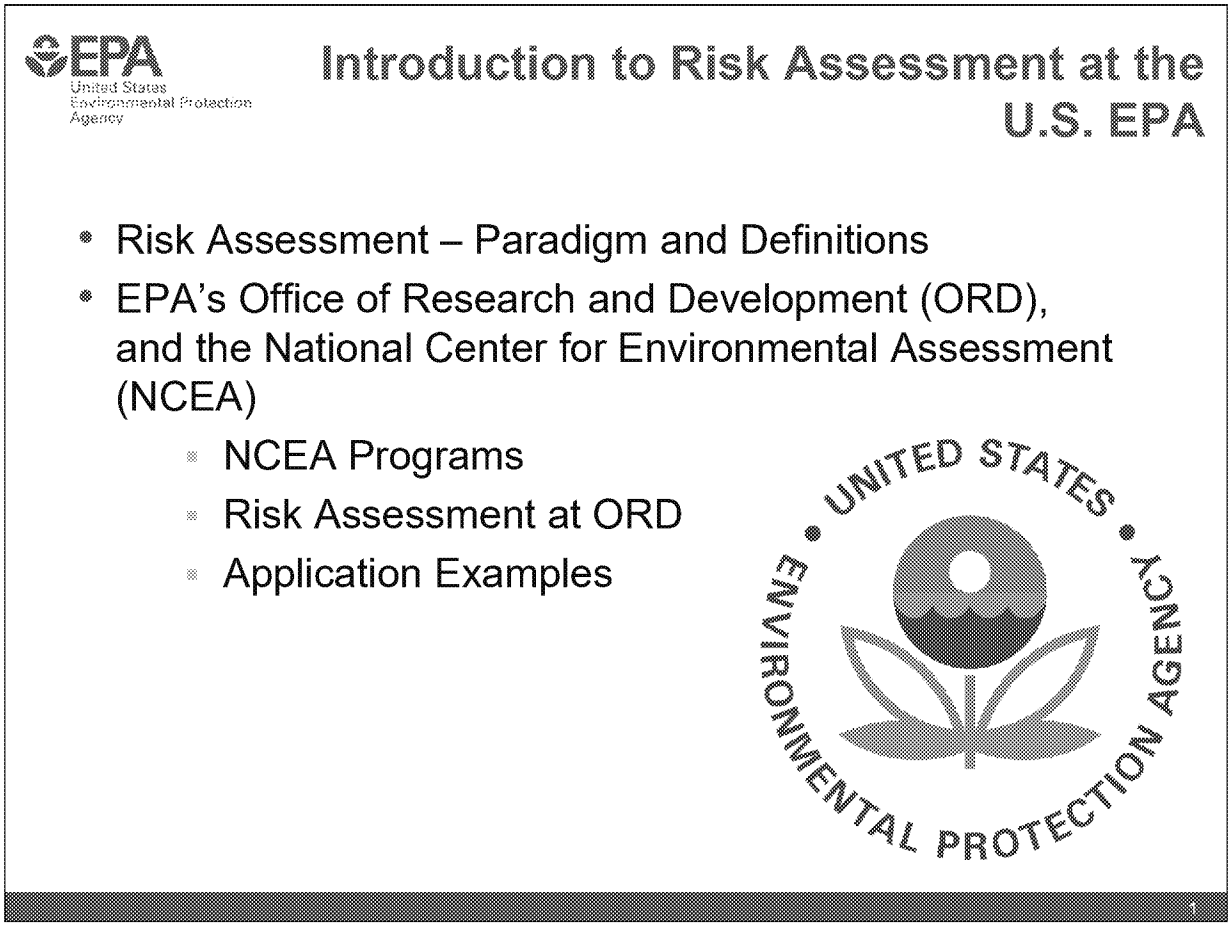
34 slides



Some basic fundamental concepts and terminology associated with risk assessment, including how the federal government applies the risk assessment paradigm
How the risk assessment process is related to and informs risk management
And the mission and organizational structure of ORD. We'll talk about:
How ORD identifies current and future environmental problems and performs research to understand them.
How environmental research informs EPA's risk assessment goals.
And we'll discuss some examples of ORD products that are used in EPA risk assessment related activities.

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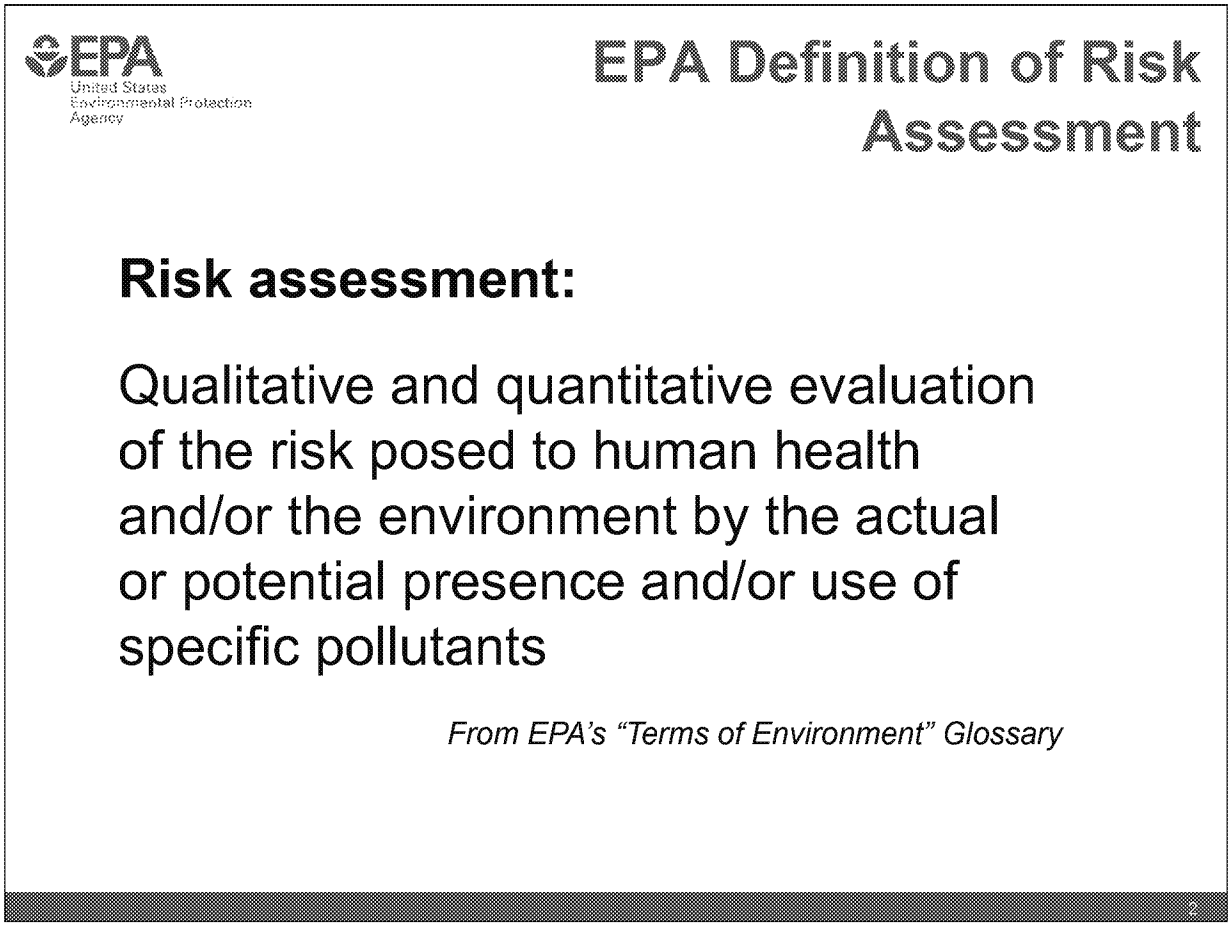
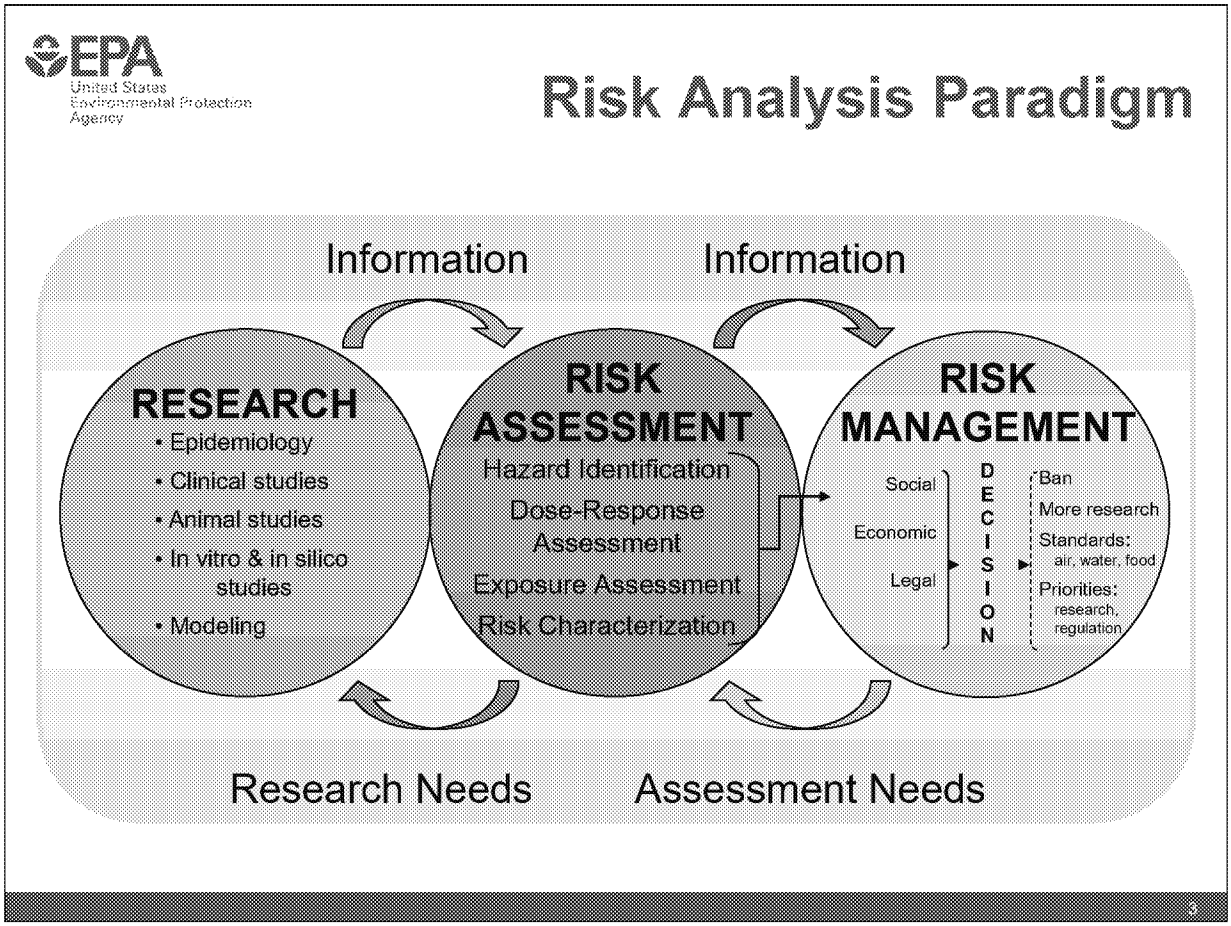


General, overarching definition.
This is a general definition from EPA's "Terms of Environment" glossary:

It says, "Risk assessment is a qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants."
How does this compare with definitions the class created earlier?
An important concept to understand is that "risk" typically refers to the probability, or likelihood, that something might happen in the future. From the Terms of the Environment glossary, risk is "a measure of the probability that damage to life, health, property, and/or the environment will occur as a result of a given hazard."
An evaluation of the current rate of disease within a population is not risk assessment; this is better described as epidemiology.
It is also important to know that risk assessment is used as a verb describing the process and also as a noun, describing the document that results from doing a risk assessment. In this course, we will typically use risk assessment as a verb.
For student reference:
This is a periodically-updated glossary of common terms; it can be found at http://www.epa.gov/glossary/.



Risk assessment as the interface between biomedical or environmental research and public or environmental health protection. Information flows forward, and assessment or research needs are communicated backwards to the risk assessment and research community.

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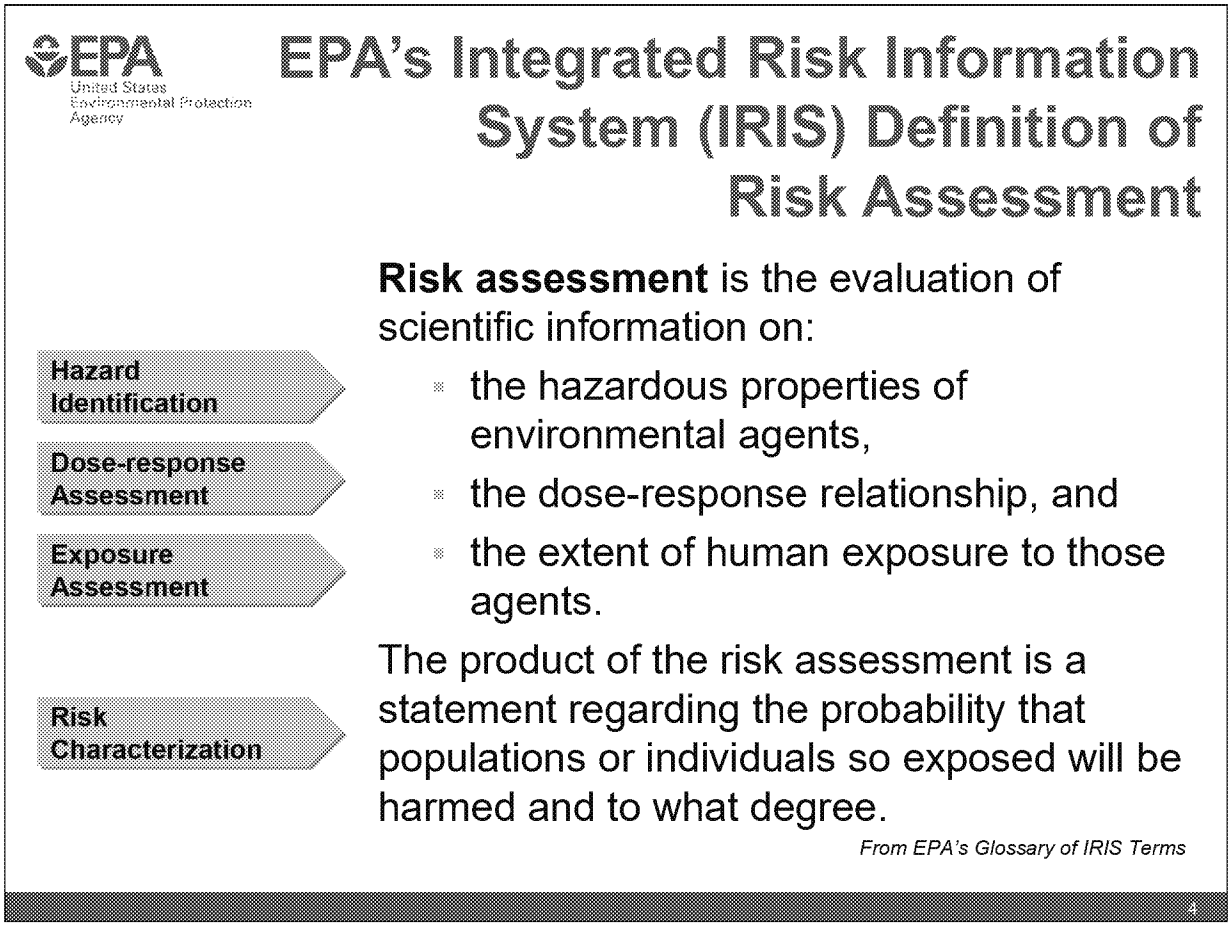

While there are differences amongst U.S. Federal Agencies in the conduct of RA, the overarching frameworks are still based upon the 4 steps described by the U.S National Research Council.
A second, expanded definition of risk assessment can be found in EPA's Glossary of IRIS Terms. We're presenting this definition because IRIS is the focus of many of the courses to come in this series.
IRIS is EPA's Integrated Risk Information System; it is an important data base of toxicity information that NCEA developed and maintains.
This definition is based on the 4 components of the risk assessment paradigm developed by the National Research Council or NRC.
Risk assessment, in terms of human health, is the evaluation of scientific information on:
the hazardous properties of environmental agents (This is hazard identification, and IRIS assessments include hazard identification.),
the dose-response relationship (This is dose-response assessment and is also included in IRIS assessments.), and
the extent of human exposure to those agents (This is exposure assessment.).
The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (This is the risk characterization component of the National Research Council's paradigm). Risk characterization synthesizes the information collected and evaluated in the other three steps.
An analogous and similar (but not identical) definition exists for ecological risk assessment.
There is variation among federal agencies regarding the conduct of RA, but the overarching frameworks that Agencies use are based on the NRC paradigm. Details can differ based on statutory requirements and history of practice within the agency.

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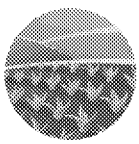
IRIS Assessments Inform Agency Decisions Under a Variety of U.S. Laws, Including:

IRIS

- Clean Air Act (CAA)
- Clean Water Act (CWA)
- Safe Drinking Water Act (SDWA)
- Food Quality Protection Act (FQPA)
- Federal Insecticide, Fungicide, and Rodenticide Control Act (FIFRA)
- Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
- Resource Conservation and Recovery Act (RCRA)
- Toxic Substances Control Act (TSCA)



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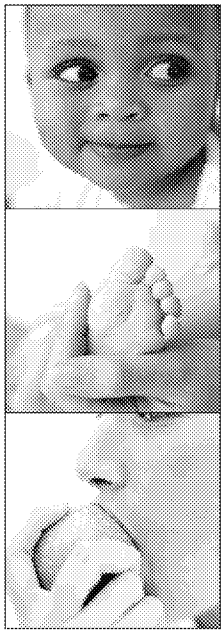
Risk Assessment is Critical to Regulatory Decision-Making

- U.S. EPA is both a regulatory agency and a science agency
- U.S. EPA operates under many laws that require the assessment of potential risk from exposure to environmental contaminants
- Risk assessment is how EPA determines risks from exposure to environmental contaminants, and is crucial for major programs in the Agency
  - E.g. air, water, waste
- Risk assessment evolves with advancement in science and new understandings about uncertainty, mode of action, metabolism, susceptibility, etc.



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Different Offices and Programs within the U.S. EPA participate in different stages or components of RA. A key point may be that risk assessment evolves (including understanding of exposures).

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U.S. EPA Exposure Standards

Medium	Standard	Regulated Contaminants
Air	National Ambient Air Quality Standards (**NAAQS**)	6 Criteria Pollutants in ambient air
	Permissible Exposure Limits (**PELs**)	~500 contaminants in workplace air
Water	Maximum Contaminant Levels (**MCLs**)	90 chemical, microbiological, radiological, and physical contaminants in drinking water
	Water Quality Criteria	For over 150 pollutants in surface waters, can be used to set enforceable water quality standards
Food	Maximum Residue Limits (**MRLs**)	Hundreds of pesticide chemicals in food and feed commodities

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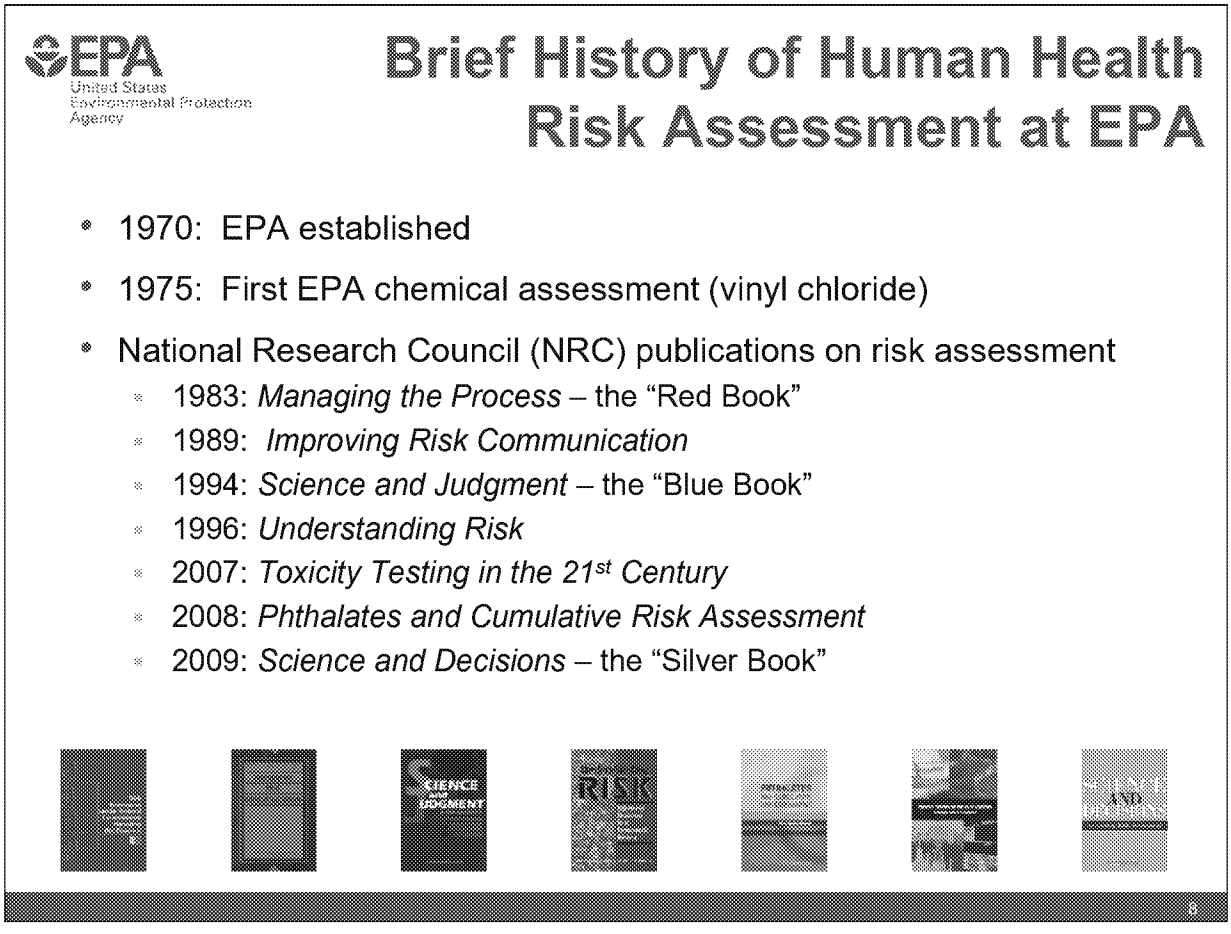
Although this table is not an exhaustive list of exposure standards developed by federal agencies, it is a large subset, demonstrating just how infrequently major exposure standards are developed.
To briefly review what is on the slide, these four standards are some of the most well-known and widely applied standards in the United States.
National Ambient Air Quality Standards, or NAAQS, have been developed for only 6 principal pollutants (called criteria pollutants) in ambient air.
Permissible Exposure Levels, or PELs, on the other hand, have been developed for over 500 contaminants in workplace air.
Maximum Contaminant Levels, or MCLs, have been developed for 90 contaminants in drinking water, but this does not apply to surface water, which we will also discuss later in this course.
Notice that no standards have been set for soil – due in part to the difficulty of establishing a standard for such a complex and variable medium.
Last on this list, Maximum Residue Limits, or MRLs, are "tolerances" set for pesticide residues in food. Over 450 pesticides have been assigned tolerances or tolerance exemptions.
Notice on this slide that most of these exposure standards have been developed by the U.S. Environmental Protection Agency, with one developed by the U.S. Department of Labor's Occupational Safety and Health Administration. As we discussed in the previous slide, only federal, state, or tribal governments can pass legally enforceable standards.



Brief History of Human Health Risk Assessment
This is not a comprehensive history but rather an overview of some key events in the timeline of chemical, human health risk assessment as it relates to EPA.
EPA was established in 1970.
EPA completed its first risk assessment document in December 1975.
Reports of cases of liver cancer (many resulting in death) in workers at vinyl chloride facilities were reported in the media in the early 1970s. Some cases of angiosarcoma were reported in people who lived in the vicinity of facilities producing vinyl chloride.
OSHA lowered permissible levels protecting workers, and EPA assessed the need to limit emissions of vinyl chloride into the air from these facilities.
EPA published the "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride."
Followed in 1976 by "Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens" published by EPA Administrator (these were not formal guidelines or policy, but were the beginnings of such guidelines)
As a scientific field, risk assessment continued to evolve – for example, the Society for Risk Analysis (SRA) published the first issue of Risk Analysis in 1981.
Then, between 1983 and 2009, the National Research Council (a part of the National Academy of Sciences) published several documents that are key to risk assessment.
The first book, published in 1983 was titled Risk Assessment in the Federal Government: Managing the Process. You may hear it referred to as the "Red Book" because of the color of its cover.
NRC was commissioned by Congress to prepare this set of recommendations
Book contains definitions and fundamental processes still in use today
This book introduced the risk assessment paradigm with its four traditional components:
Hazard Identification
Dose-response Assessment
Exposure Assessment
Risk Characterization
1994 - Science and Judgment in Risk Assessment, aka the "Blue Book"
Also commissioned by Congress (via Clean Air Act)

In part, a follow-up to the Red Book, but with specific emphasis on EPA's scientific methods
2009 - Science and Decisions: Advancing Risk Assessment, aka the "Silver Book"
Discusses the planning and scoping principles of risk assessment along with stakeholder involvement, with EPA in mind
Other NRC publications on risk assessment include:
1989: Improving Risk Communication
1996: Understanding Risk
2007: Toxicity Testing in the 21st Century
2008: Phthalates and Cumulative Risk Assessment

The next several slides cover definitions and terminology related to the four primary components of the risk assessment paradigm.

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Important Risk Assessment Definitions:
Hazard

The inherent toxicity of a compound. Hazard identification of a given substance is an informed judgment based on verifiable toxicity data from animal models or human studies.

(EPA's Glossary of Terms of the Environment)

E.g., a shark, swimming in an aquarium

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There are multiple definitions for hazard, but in general, hazard addresses the question, "what kind of harm are you dealing with?"
Hazard identification determines the nature of effects produced by an agent. Does the agent or chemical cause cancer or reproductive changes?
Hazard / agent / stressor may be used synonymously. Human health risk assessors usually prefer hazard or agent depending on the specifics of the risk assessment.
Some definitions consider "hazard" to be the description of the harm caused. For example the toxicity value associated with a particular compound.
Your reading packet has many definitions for hazard from the EPA thesaurus.
Another example of inherent property:
Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent. (IPCS/OECD 2004)
International Programme on Chemical Safety / Organisation for Economic Co-operation and Development (OECD)
This last example definition brings in the concept that an exposure is required for harm to happen.

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Important Risk Assessment Definitions: Exposure

Quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).

From EPA's IRIS Glossary

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Exposure answers the question "how much of a substance is an individual (or population) exposed to?"

Contact is required for exposure, and without exposure, there is no dose.

Contact is made between the chemical, physical, or biological agent and the outer boundary of the organism. The outer boundary might be the skin, lungs, or gut.

A concentration in the environment doesn't become a dose until exposure occurs.

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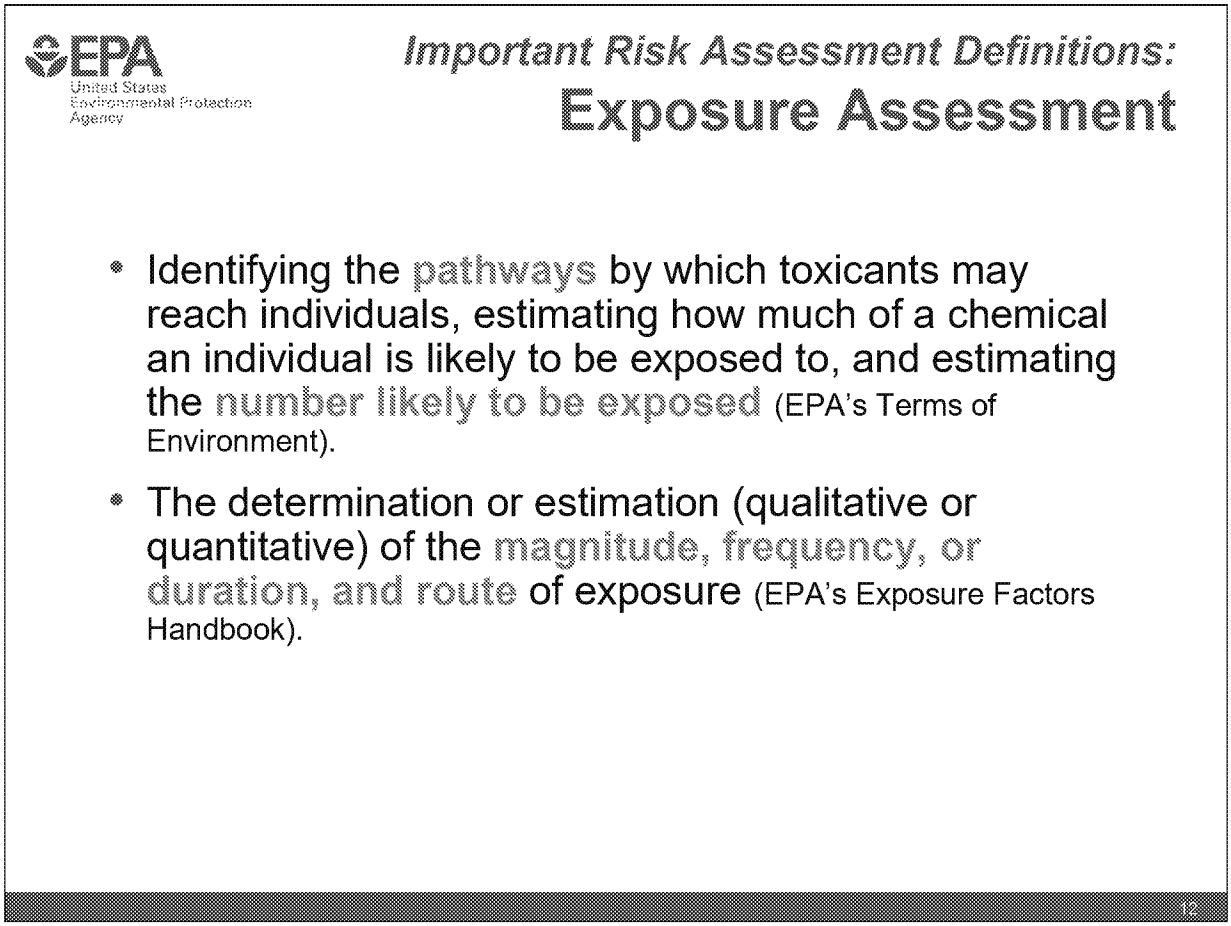

An exposure assessment is the process of estimating the magnitude (dose), frequency (daily, or event based), and duration (how long) of human (or animal) exposure to a substance.

An exposure assessment considers the:
Exposure pathway – The physical course (e.g., through the air or water) that a chemical takes from its emission by the facility to the exposed individual and is related to the type of release (how the chemical enters the environment)
Exposure route - The way a chemical enters an organism after contact (e.g., by ingestion, inhalation, dermal absorption).
Exposure media - Material (e.g., air, water, soil, food, consumer products) surrounding or containing an agent.
Media is captured in pathway.
Exposure source - An entity or action that releases a stressor to the environment (or imposes a stressor on the environment).
Origin of an agent.

The size and often the characteristics (e.g., age, pre-existing disease) of the population are also considered..

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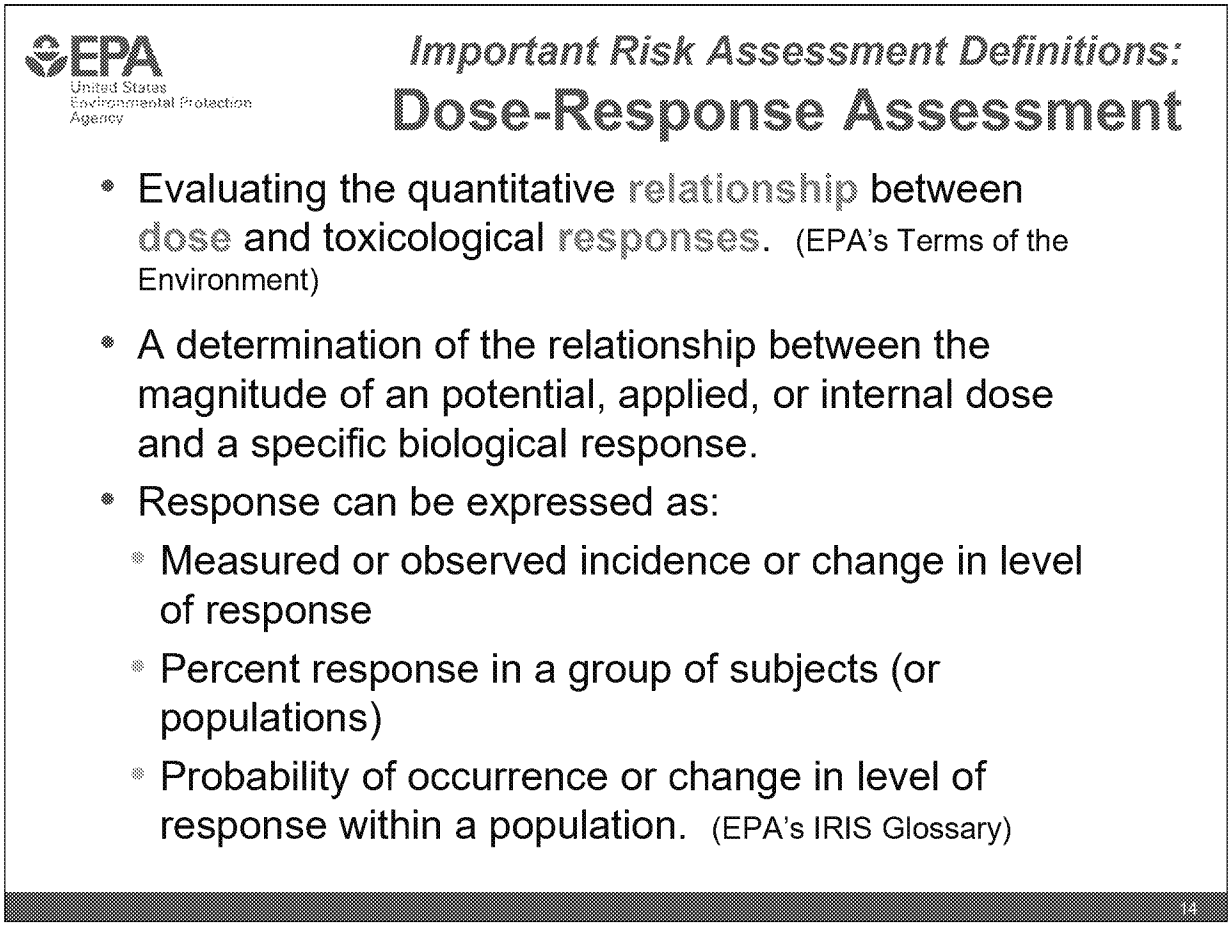
Important Risk Assessment Definitions: Dose

- The amount of substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.
  - **Potential dose** is the amount of substance ingested, inhaled, or applied to skin, not all of which will be absorbed.
  - **Applied dose** is the amount of substance at an absorption barrier (skin, respiratory tract, gut) that can be absorbed by the body.
  - **Internal dose** is the amount of substance absorbed and available for interaction with biological receptors.



Dose-response assessment is sometimes called "Toxicity Assessment." A dose-response assessment evaluates the relationship between the dose (or amount) of a chemical and the corresponding effects. A dose-response assessment attempts to answer the question, "how much of a chemical can an individual be exposed to without seeing effects" or in other words "what is a generally safe dose?"

Dose-response assessments are the primary piece of the risk assessment paradigm that IRIS scientists work on.

A key concept in dose-response is that it is a relationship between the dose and the effect seen or expected to occur in animals or humans. This is the basic idea that health responses are not simply yes or no, but there is a continuum of responses.

Note that the term response captures a lot of different ways to look at response:
Measured or observed incidence or change in level of a response (can be a continuous measure or a snapshot in time)
Change in level or type of response (may be symptom or level of severity)
Population based: A percent response in a group of subjects (or populations)
Probability-based: Probability of occurrence or change in the level of response within a population.

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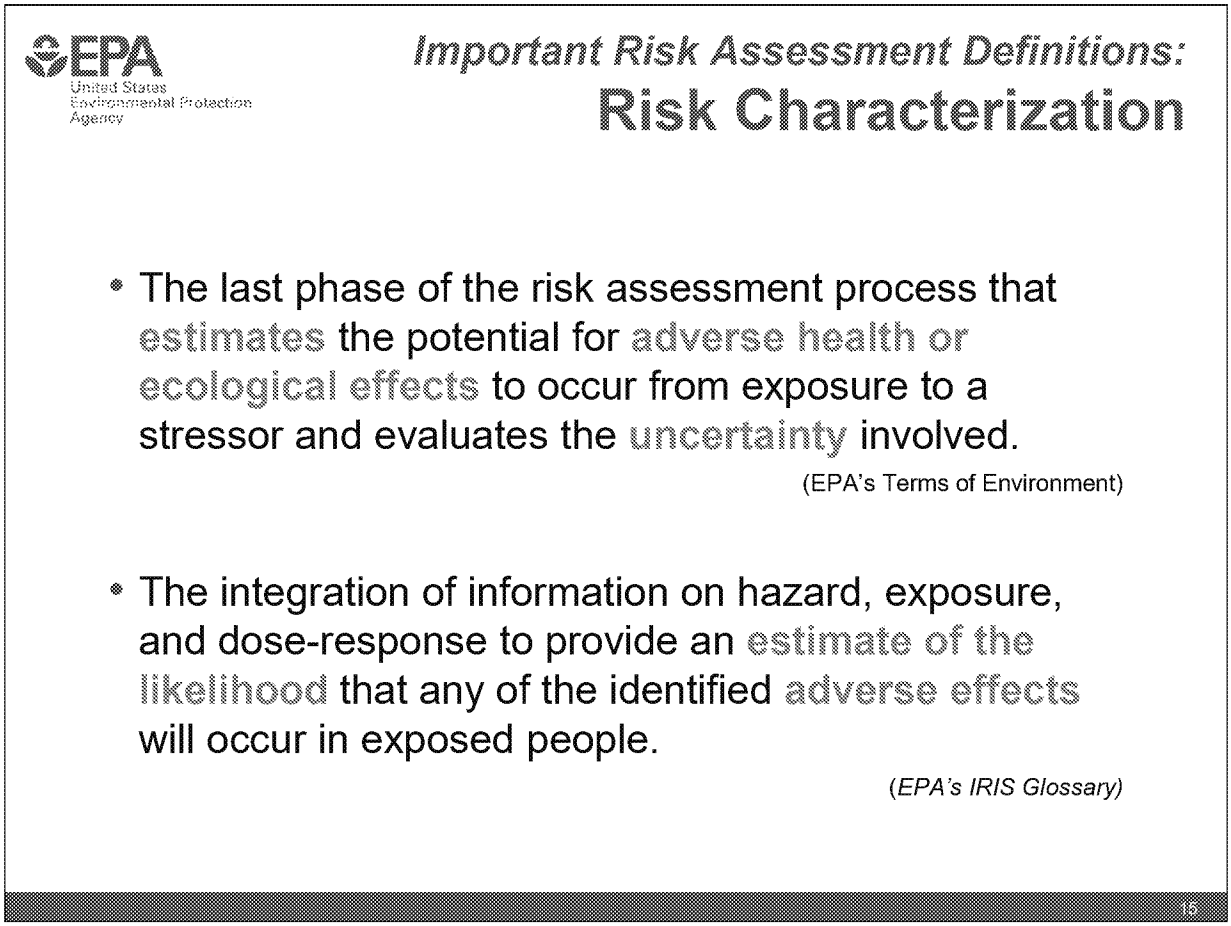

Finally, risk characterization integrates the hazard identification, exposure assessment, and dose-response assessment components to estimate the potential for adverse health or ecological effects resulting from exposure.

Uncertainty analysis is also incorporated in the risk characterization component of the risk assessment paradigm. Our uncertainty depends on the data we used in the previous four components of the process. For example, if we used dose-response data for mice and extrapolated those results to humans, our uncertainty will be higher than if we were basing our dose-response assessment on epidemiological or clinical study data. Our uncertainty might be expressed and applied as a number, for example, an uncertainty factor, but it will also be described qualitatively.

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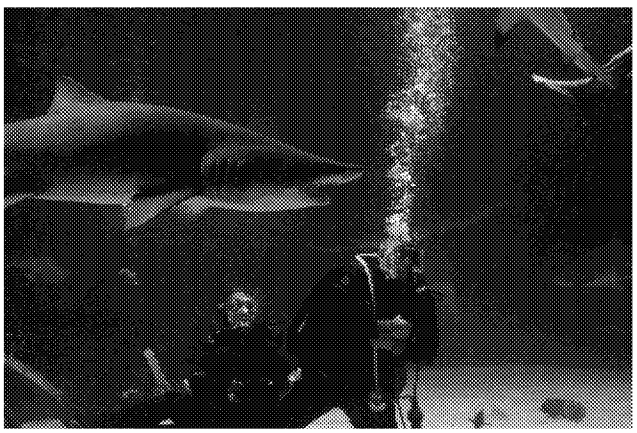
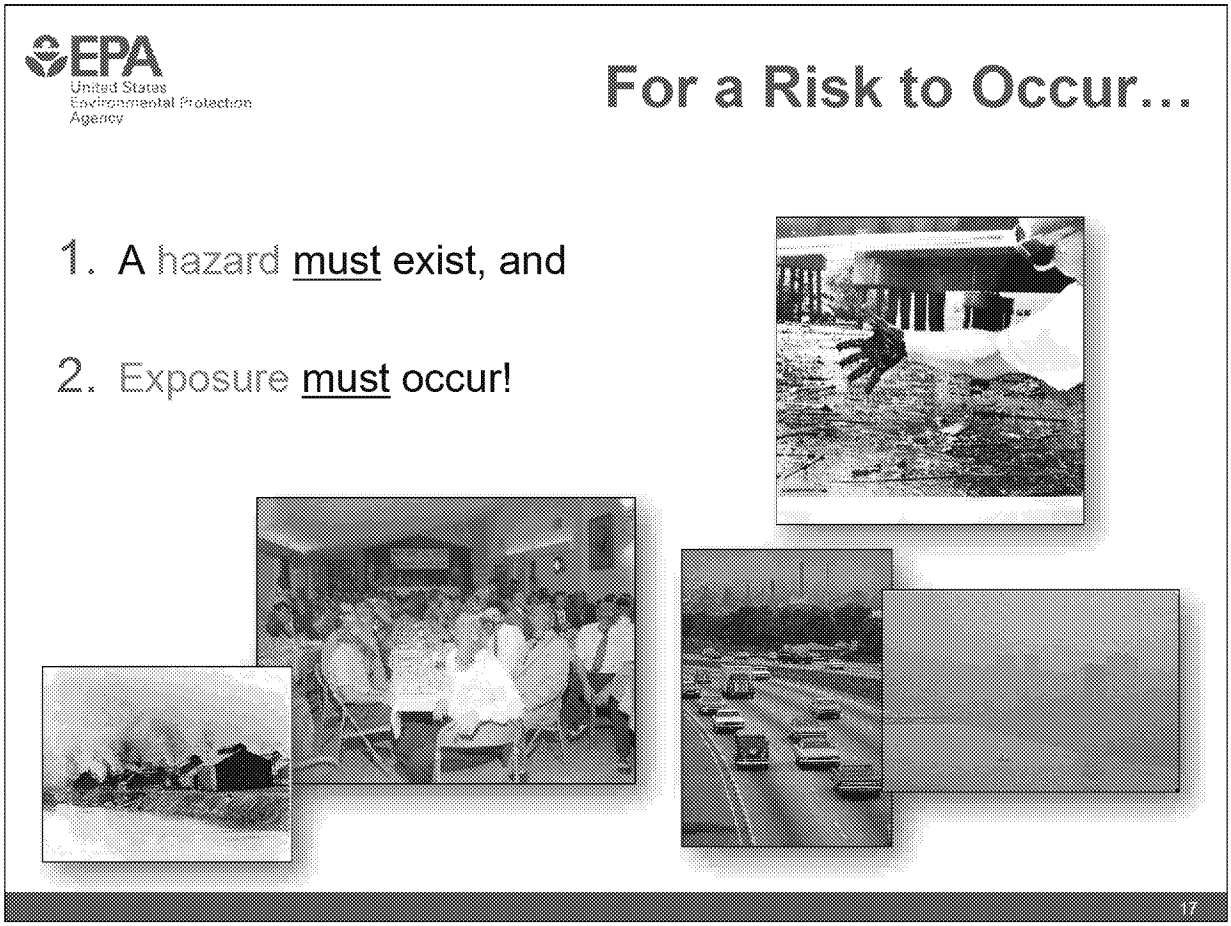
Important Risk Assessment Definitions: Risk

The hazard which may result from an internal dose following specific levels of exposure to compound, or mixture of compounds.

E.g., swimming WITH the shark in an aquarium





Question for the class?

Can you think of any other hazard/risk scenarios? – they can be chemical, biological, physical, or natural.

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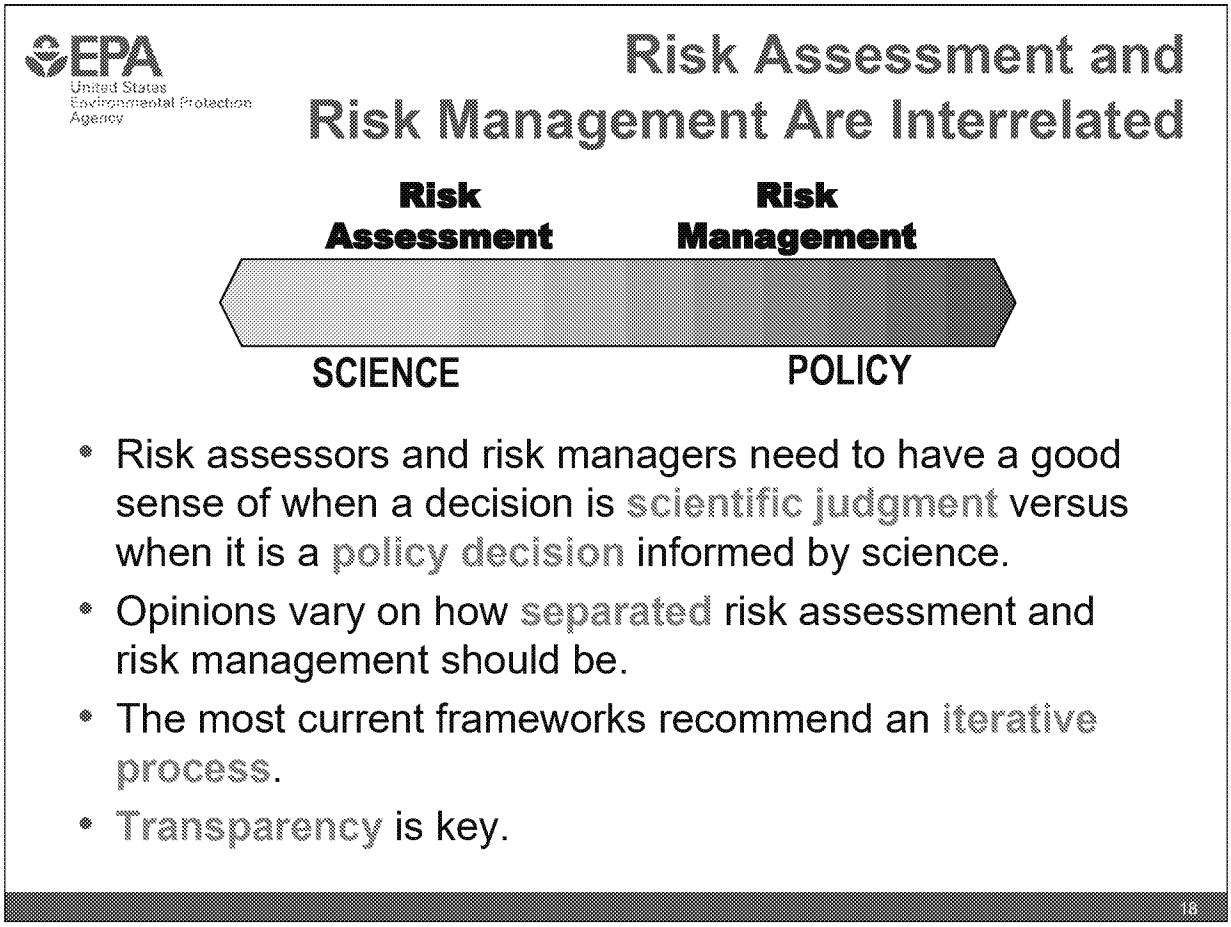

Risk assessment and risk management are two components of the risk analysis paradigm introduced earlier (along with risk communication). Recall that the circles for each of these overlap.

In conducting a risk assessment and using the results to make a risk-based decision, there is typically a continuum of decisions ranging from those that are clearly scientific judgment to those that are clearly policy decision. But then there are some decisions that are made during risk assessment that fall in the grey zone. In these cases it may be uncomfortable for either risk managers or risk assessors to claim the decision.

Early on risk assessment and risk management were so interwoven the process lacked transparency. There was a push to separate RM from RA was so that these 2 types of decisions would not be confused. So the separation of RM and RA became very deliberate and as complete as possible.

The current trend, however, is to recognize that the process is iterative, so risk managers and risk assessors communicate and work together but there is also transparency regarding what aspects of the decision and process are risk managements and what aspects are risk assessment.

Risk assessment is a non-linear process, as we saw in the Superfund illustration earlier, and it may be also an iterative process.
This involves a dialog between risk assessors and risk managers about the scope of the risk assessment.
Risk assessors and risk managers work together to develop the questions the RA will address.
The iterative process can also include screening level risk assessments that can help pare down the scope of a detailed quantitative risk assessment.
Successive iterations of RA can incorporate new information on risk management options and risk mitigation approaches.
Finally, transparency is "Conducting a risk assessment in such a manner that all of the scientific analyses, uncertainties, assumptions, and science policies which underlie the decisions made throughout the risk assessment are clearly stated (i.e., made readily apparent)." For instructor reference: EPA Air Toxics Risk Assessment Reference Library.
The examples presented at the end of this course illustrate how risk assessment informs risk management.

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Three Types of Assessments, Three Different Purposes

All three incorporate a variant of hazard characterization

- Risk Assessment combines hazard characterization with exposure assessment to determine potential for adverse effect of a chemical
  - May address what levels are association with no/low risk i.e., reference values, or
  - Determine if a risk exists in a specific site or exposure scenario
- Alternatives Assessment identifies, evaluates and compares hazard of chemicals across a similar use or exposure based on a chemical that is a known risk, e.g., PBDE flame retardant, for purpose of selecting a safer chemical
- Life Cycle Assessment measures or estimates the total impacts of resource extraction, energy use, water use, chemical emissions and more, across a chemical or product life cycle (resource extraction, chemical synthesis, use, disposal) to identify how to reduce overall environmental footprint of a product

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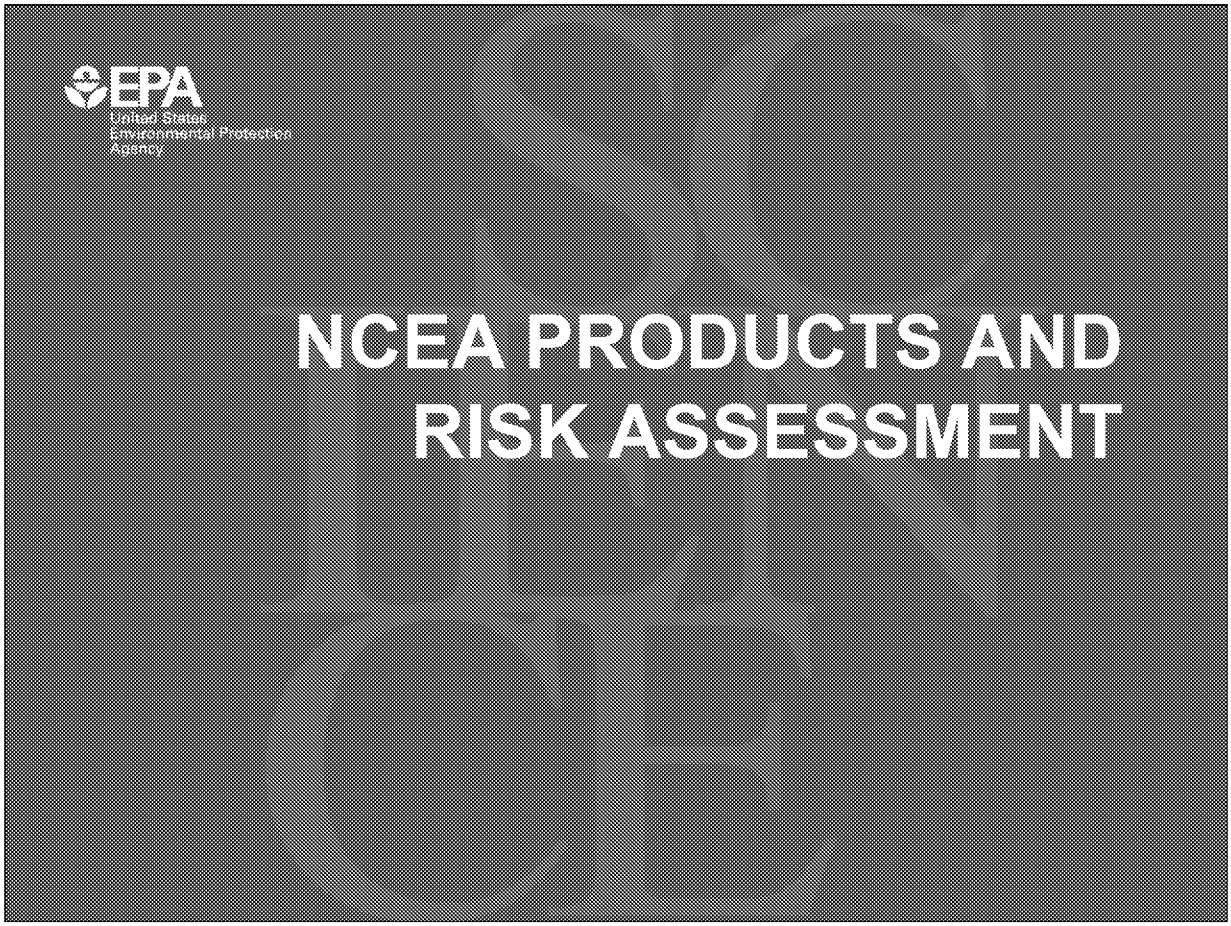
Other relevant websites:
EPA DfE/Safer Choice:
https://www.epa.gov/saferchoice/design-environment-alternatives-assessments#tab-2



Now that we all have a common vocabulary to use to talk about risk assessment, we'll talk about how EPA's Office of Research and Development, and specifically, the National Center for Environmental Assessment, contributes to risk assessment and risk management at EPA.

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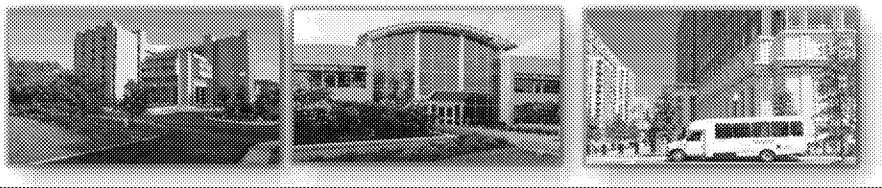
National Center for Environmental Assessment (NCEA)

- The mission of NCEA is to provide guidance (assessments and guidelines) about how pollutants may impact human health and the environment.
- NCEA occupies a critical position between scientists in ORD and management in EPA's program and regional offices supporting regulatory, enforcement, and remedial-action decisions.
- NCEA administers numerous high-profile programs: the Global Change Research Program, the Report on the Environment (ROE Database), Integrated Science Assessment (ISA) and the Integrated Risk Information System (IRIS) Program & Database.
- NCEA's diverse staff includes biologists, chemists, ecologists, engineers, epidemiologists, geneticists, statisticians, and toxicologists.



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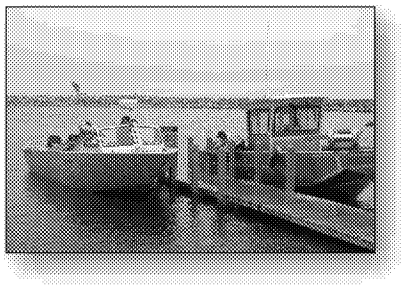
IRIS Values Used in Generation of Fish Advisories



- IRIS includes an RfD for methylmercury
- RfD combined with exposure factors and contaminant concentrations
- Result is general advice about fish consumption and location-specific advisories

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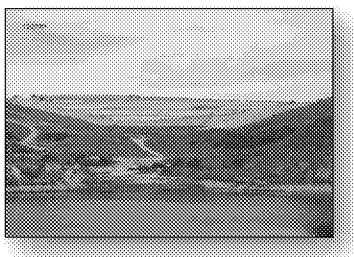
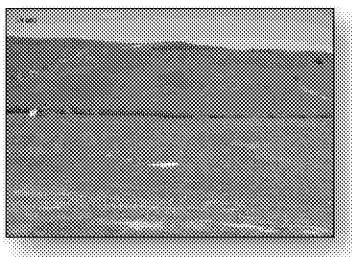
IRIS and Provisional Peer-Reviewed Toxicity Values (pPRTVs) for the Superfund Program

Casmalia Resources in Santa Barbara County, CA

- Former hazardous waste management facility
- Chemicals of concern include pesticides, solvents, acids (including hydrogen sulfide), PCBs, and heavy metals
- NCEA values support decisions about remedial actions including landfill covers, groundwater monitoring, and site improvements


Integrated Science Assessments

- EPA has set National Ambient Air Quality Standards (NAAQS) for six principal air pollutants, which include: Carbon Monoxide, Lead, Nitrogen Dioxide, Ozone, Particulate Matter, Sulfur Dioxide

- Numerous sources emit these "criteria pollutants", which are considered harmful to public health and the environment. Since 2008, EPA's Integrated Science Assessments (ISAs) have formed the scientific foundation for the review of the NAAQS standards.

- Prior to 2008, Air Quality Criteria Documents provided the scientific foundation for the NAAQS process; as part of a streamlining of the NAAQS process these documents were replaced by the ISAs.

The ISA accurately reflects "the latest scientific knowledge useful in indicating the kind and extent of identifiable effects on public health which may be expected from the presence of [a] pollutant in ambient air." (Clean Air Act, Section 108, 2003)

Assess Environmental Condition

- Emission Inventory – Stationary and Mobile Sources

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NCEA products are also used along with, and to support, environmental emissions monitoring.

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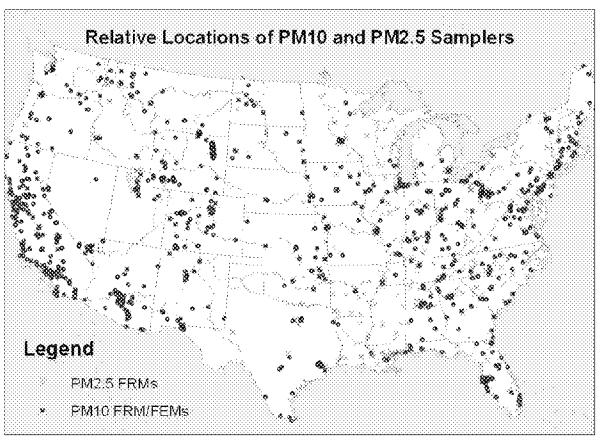
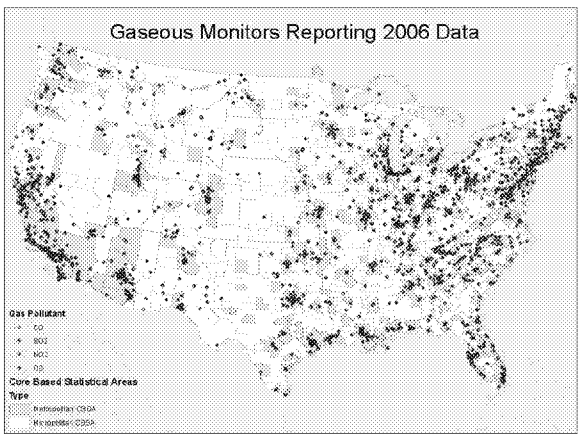
Assess Environmental Condition

- Monitoring - ~$170 Million per year spent on air monitoring in United States





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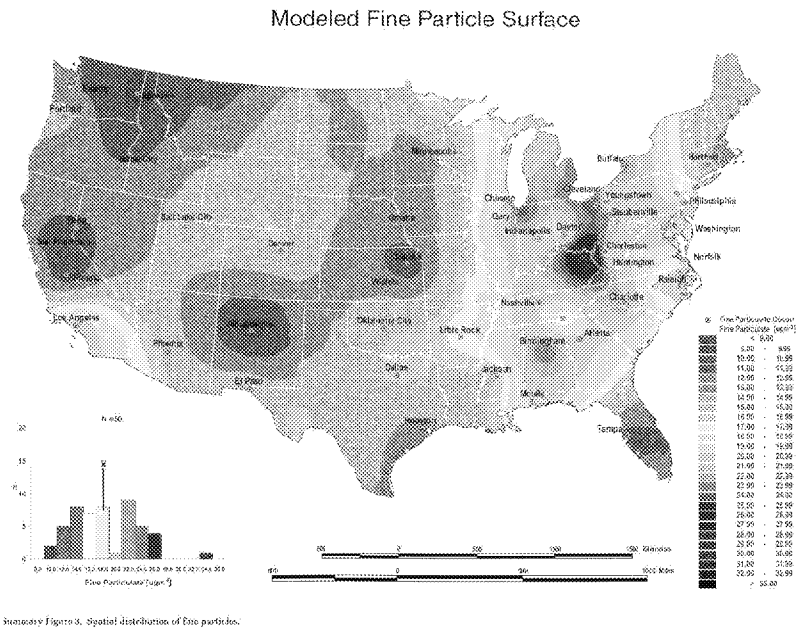
Assess Environmental Condition

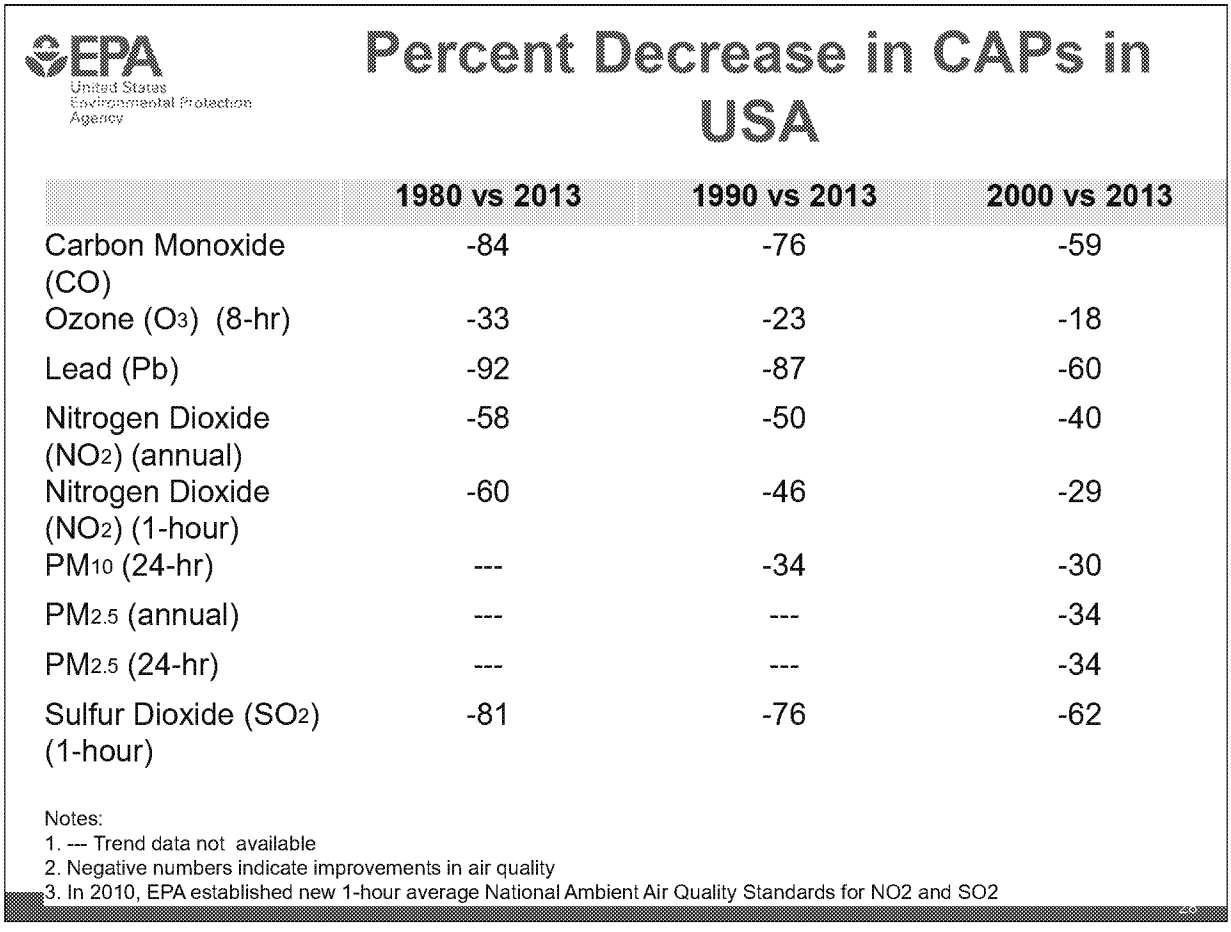
Modeling:

- Relate emissions to concentrations
- Predict concentrations in areas without monitors



1999 Annual Mean PM2.5 as of July 6, 2000

Despite widespread air monitoring, significant gaps in coverage remain – and modeling can be used to estimate air concentrations.



Criteria air pollutants (CAPs).

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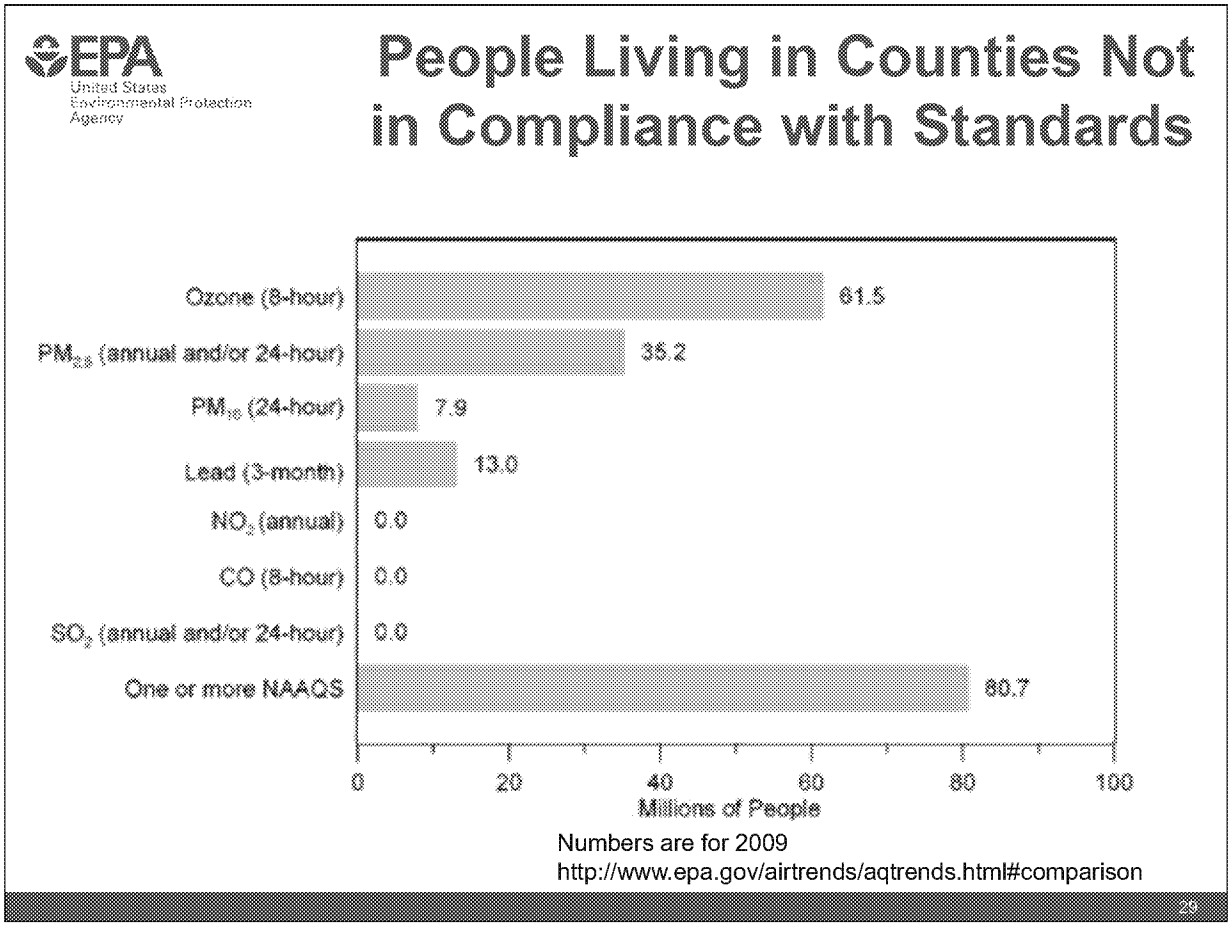

Despite significant improvement in the air quality overall, there is still need for significant improvement in specific areas with high levels of various CAPs.

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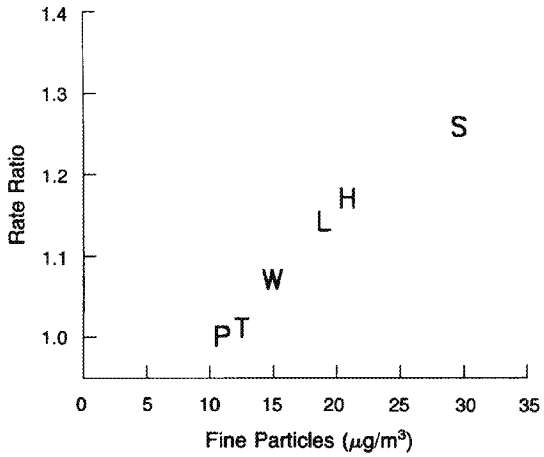
Harvard Six Cities Study

- Risk of dying increases as fine PM concentrations increase

The NEW ENGLAND JOURNAL of MEDICINE

An Association Between Air Pollution and Mortality in Six U.S. Cities

Dockery DW, Pope CA III, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, Speizer FE.



P: Portage, T: Topeka, W: Watertown
L: St. Louis, H: Harriman, S: Steubenville

30

One example of the need for continued vigilance and improvement in air quality: the Harvard study associating increased air Fine PM content with increased mortality.

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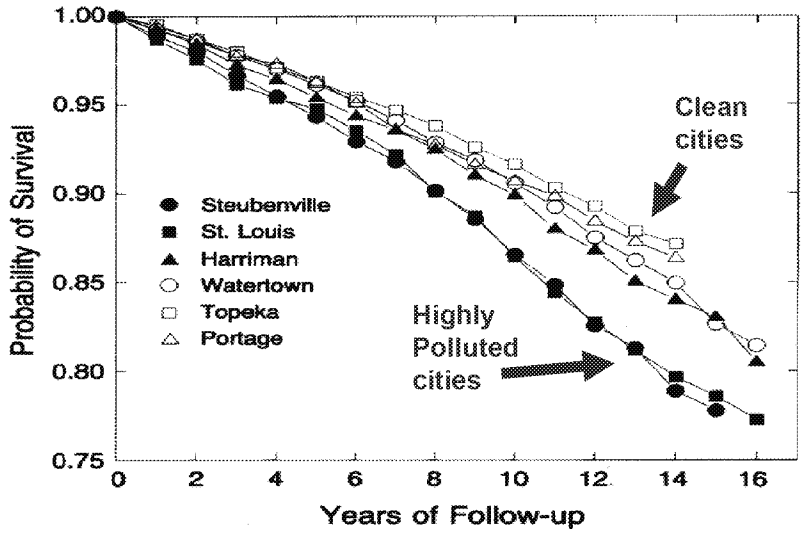
Harvard Six Cities Study

- Living in U.S. cities with poorer air quality is associated with shorter lifespan



31

joke You will note from this graph that survival decreases in populations from each of the 6 cities – I'm sorry to say, that we haven't figured out how to keep people alive forever, even with cleaner air.
But, more seriously, in addition to specific associations between Fine PM content and mortality, there is also a general association between higher level of CAPs (i.e. poorer air quality) and increased mortality.

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And now we'll briefly look at two examples of how risk assessment and risk management can be used as part of a cost-benefit analysis to inform the decision-making process – and that environmental health protection does not necessarily inhibit economic growth and development.

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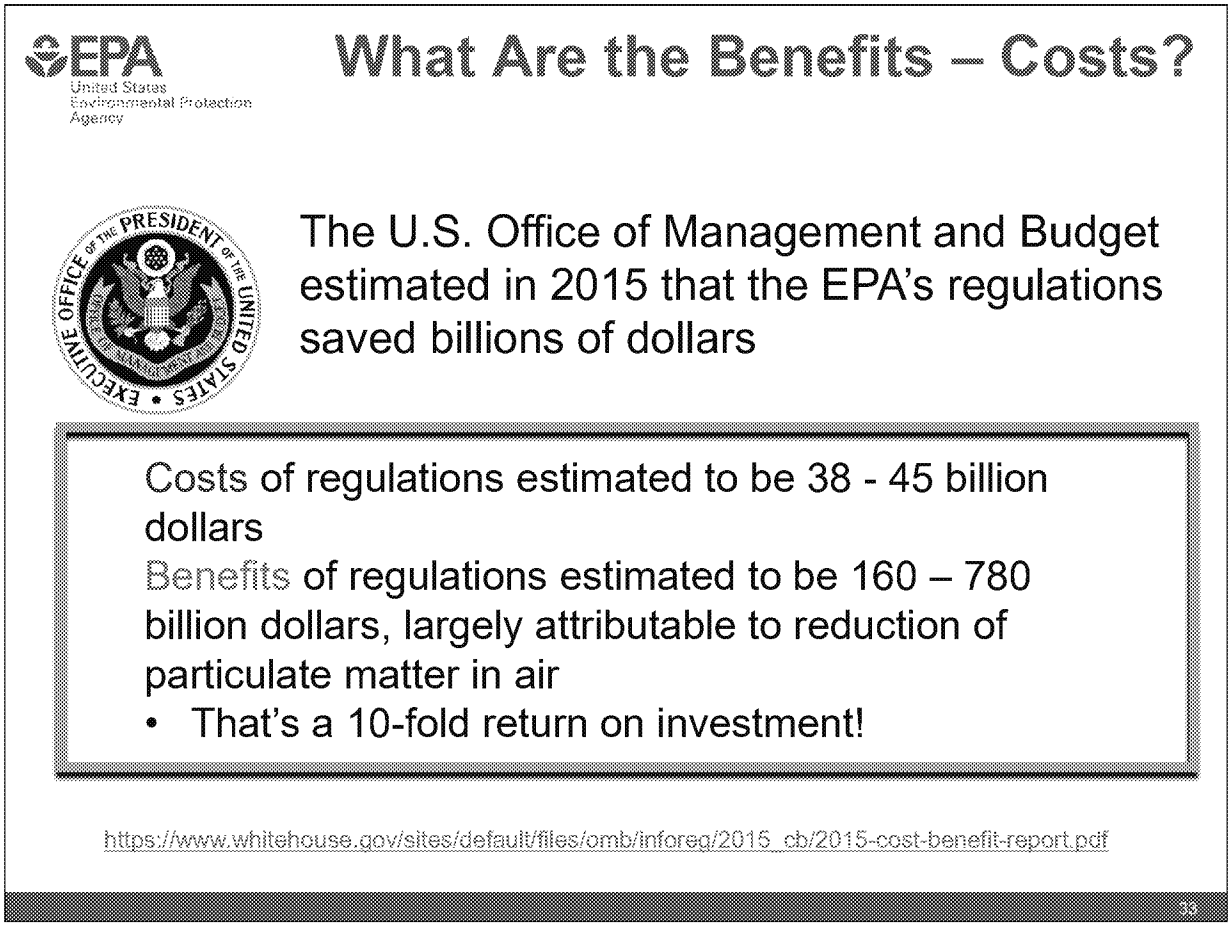
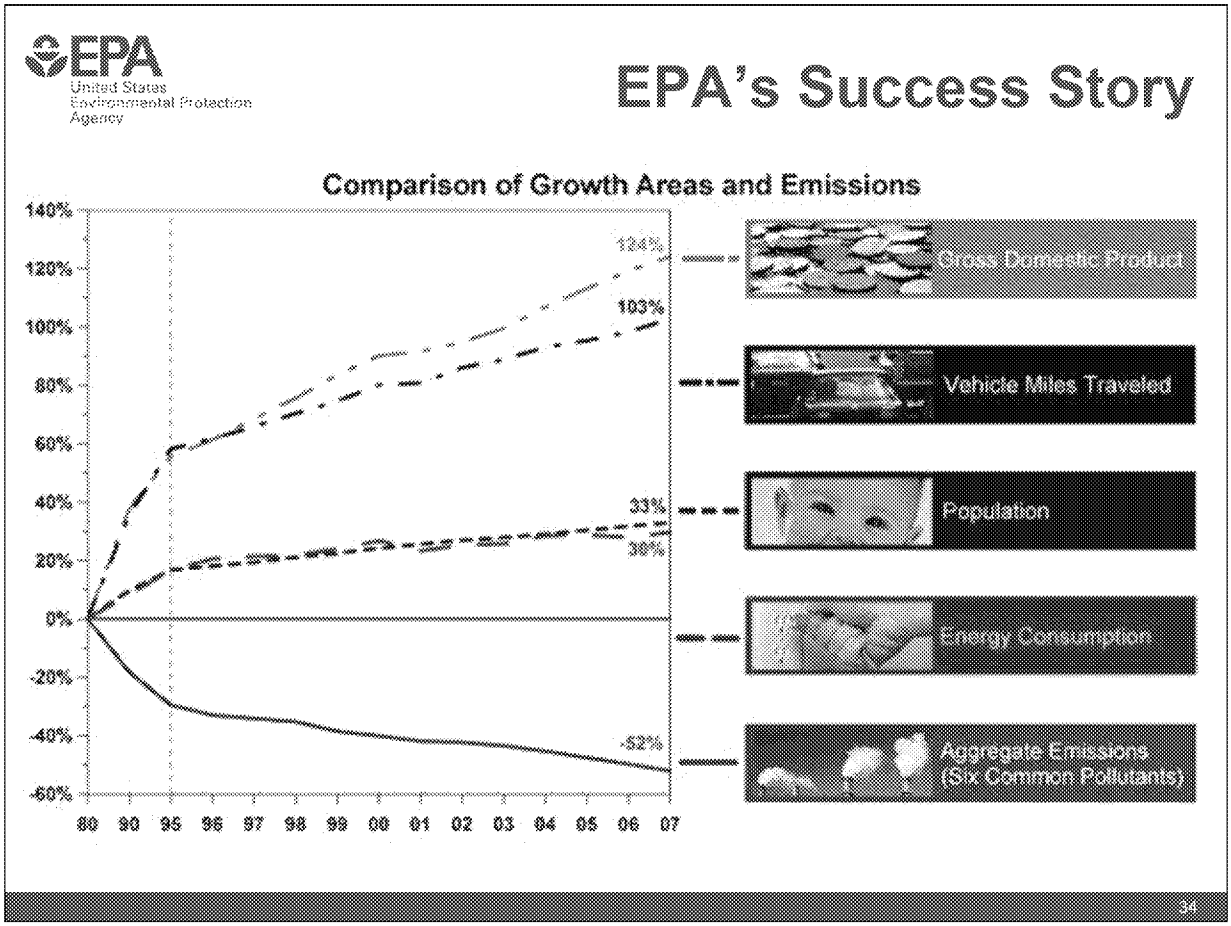


The benefits of air regulation greatly exceeded the costs.



Note the scale difference between 1980-1995: emphasis is on the ~12 year period from 1995-2007.

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MINISTRY OF ENVIRONMENTAL PROTECTION
THE PEOPLE'S REPUBLIC OF CHINA

Hazard Identification and Dose-Response Assessment

Environmental Health Training Program
January 2018, Guangzhou, China

Office of Research and Development
National Center for Environmental Assessment

35

39 slides

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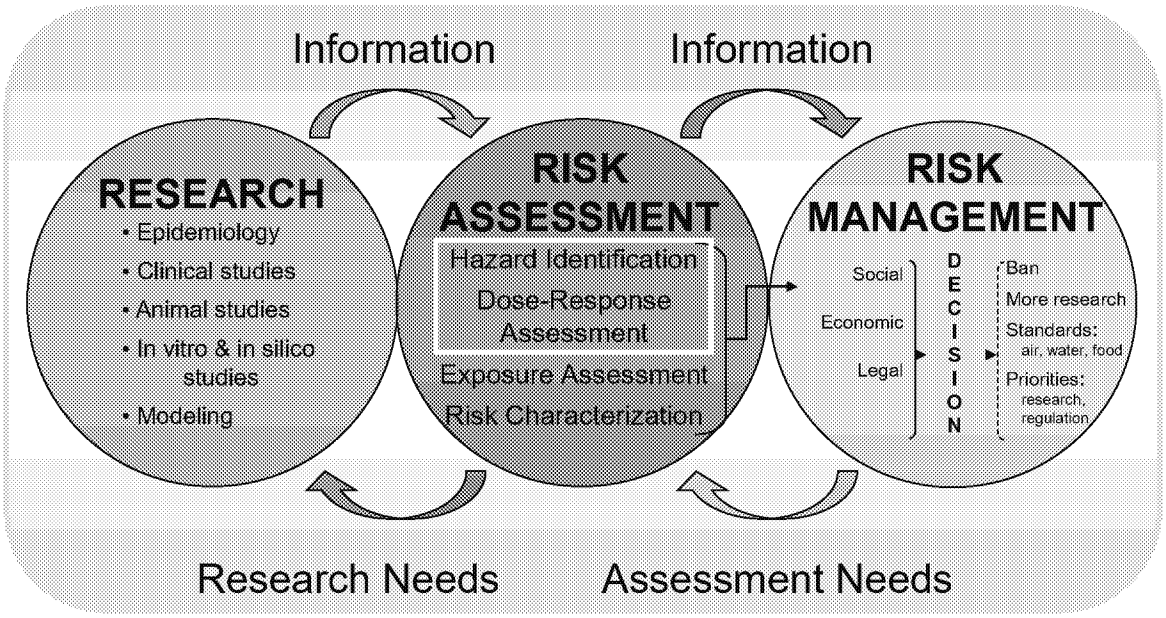
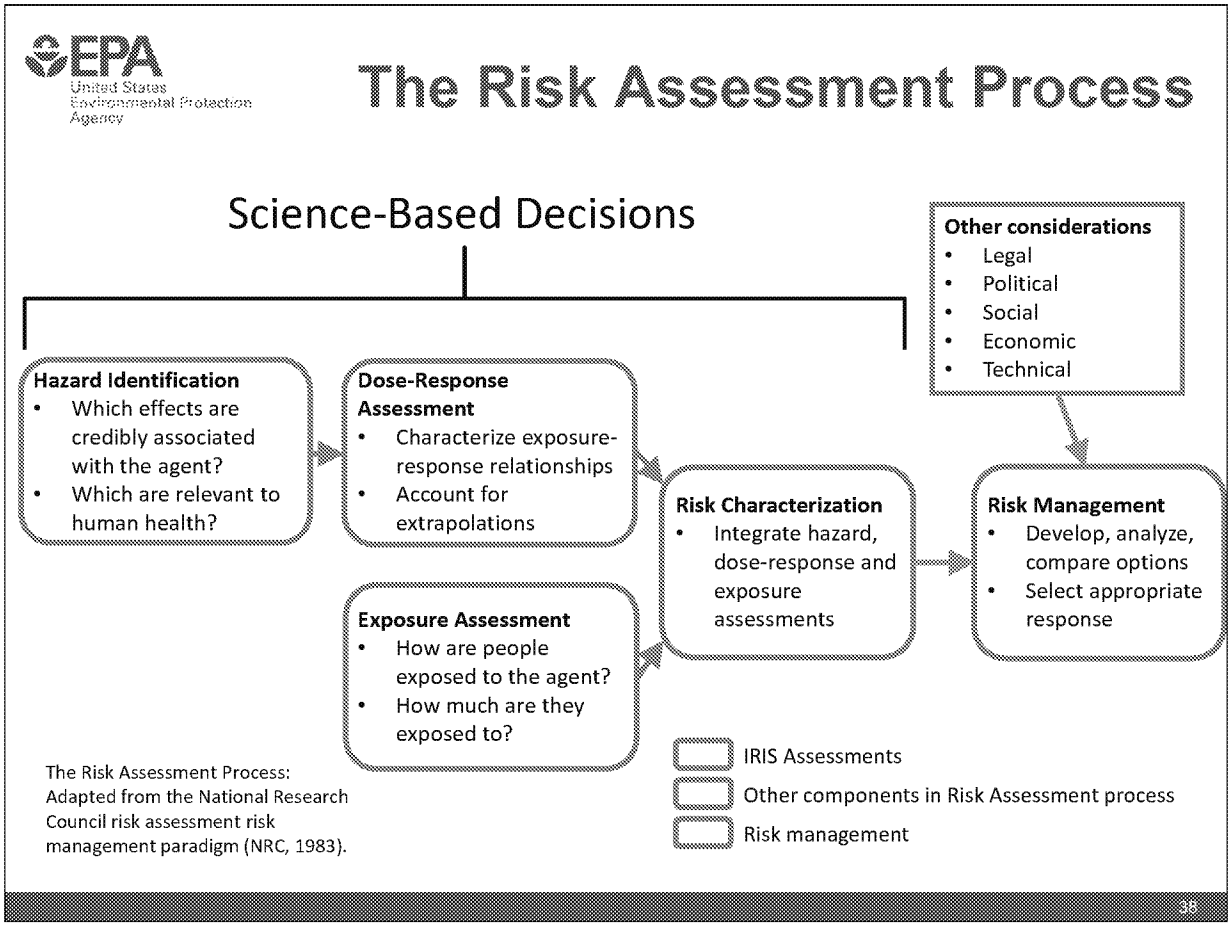
Overview of Human Health Hazard Characterization

Major topics:

- Review risk assessment process
- Review types of data used in human health risk assessment
- Discuss process involved in hazard synthesis and characterization
- Discuss main elements in dose-response assessment

Risk Assessment Paradigm





The four steps in RA are outlined here, with an emphasis on the role that science plays in the decision-making process, as opposed to other considerations which are discussed as a part of Risk Management.

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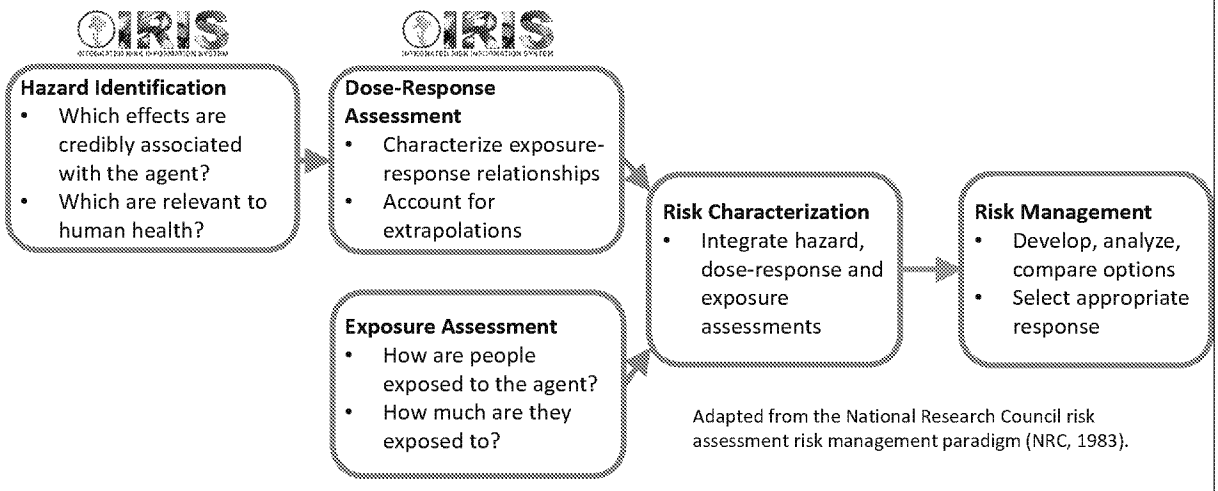
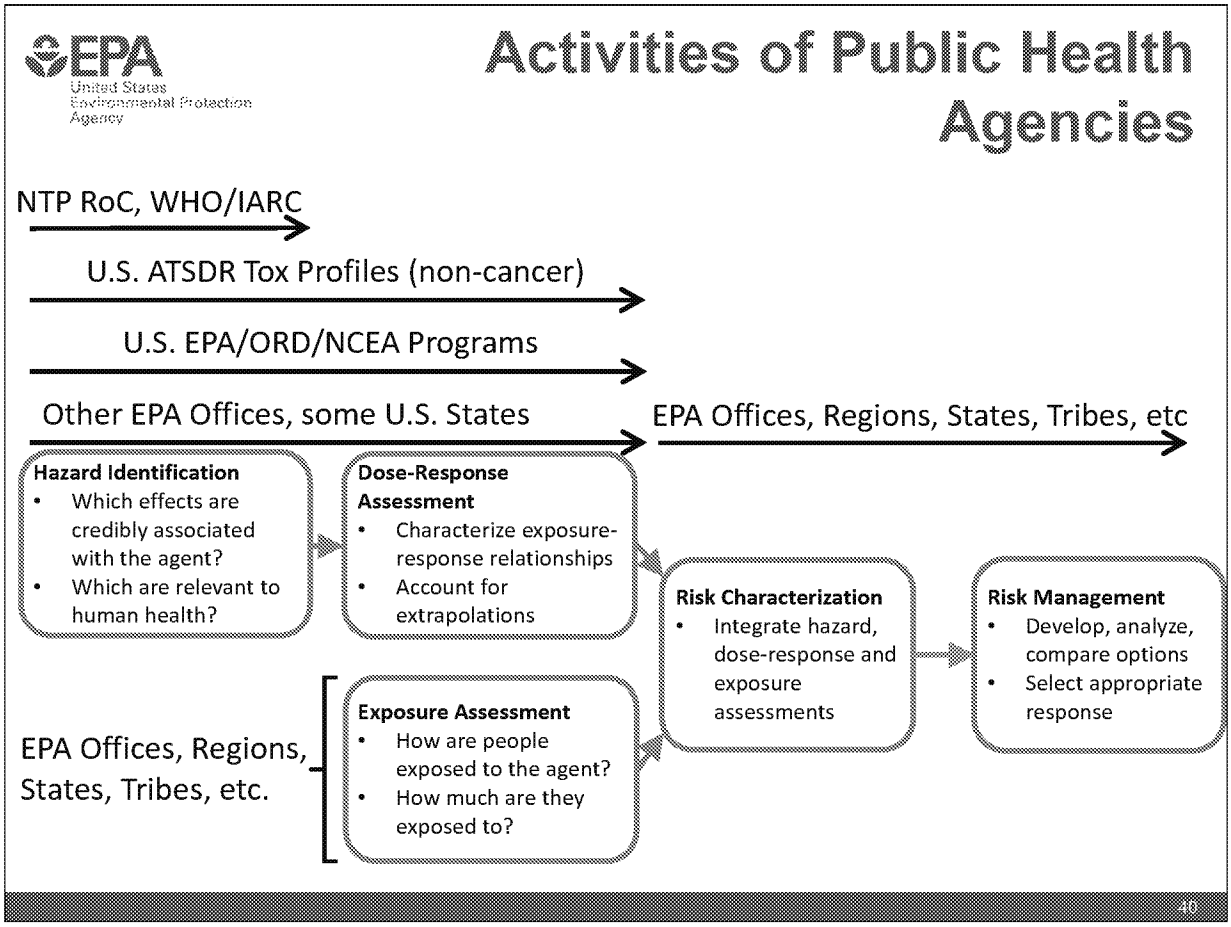
The Integrated Risk Information System (IRIS)

IRIS assessments are a systematic review of the publicly available scientific studies on environmental agents, with 2 goals:

1. Hazard Identification → nature of hazardous effects
2. Dose-Response Assessment → concentrations associated with effects



Adapted from the National Research Council risk assessment risk management paradigm (NRC, 1983).



National Toxicology Program (NTP), Report on Carcinogens (RoC), World Health Organization (WHO) International Agency for Research on Cancer (IARC), Agency for Toxic Substances and Disease Registry (ATSDR),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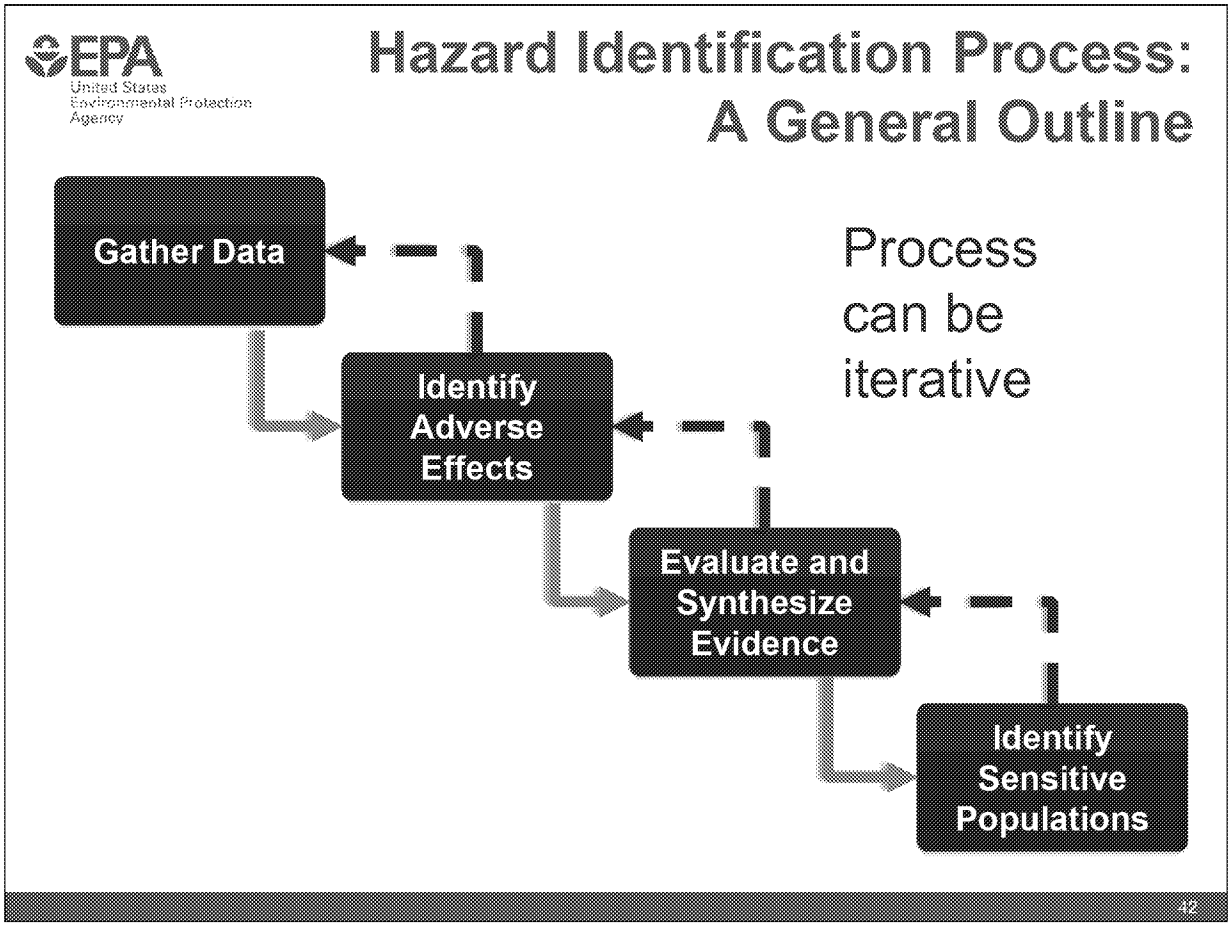
HAZARD IDENTIFICATION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Hazard Identification Process:
A General Outline
Gather Data
Identify
Adverse
Effects
Evaluate and
Synthesize
Evidence
Identify
Sensitive
Populations
Process
can be
iterative
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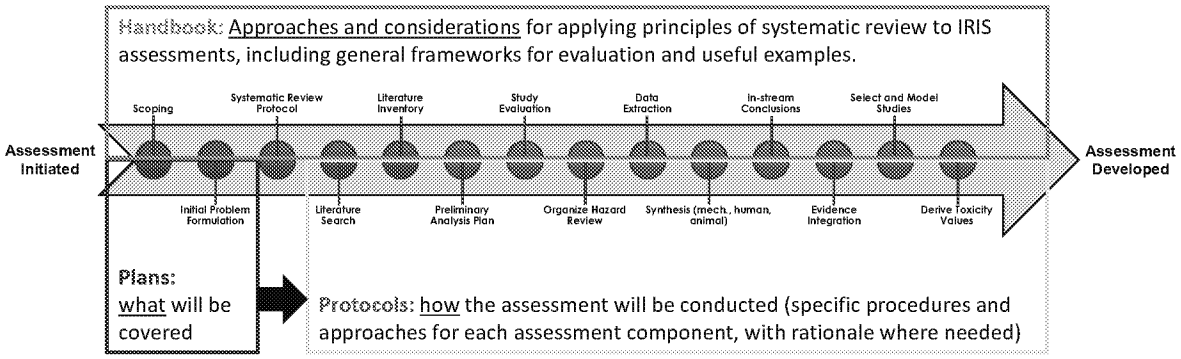
Incorporating Systematic Review Elements in Assessment Development



- Assessment development illustrated as sequential steps in the systematic review process, which promote consistency and transparency
- General standard operating procedures will be described in the IRIS Program Handbook, while chemical-specific approaches tailored to each assessment are described in the assessment plans and systematic review protocols

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In NCEA, we are currently working to adopt the principles of systematic review and apply them to all of our environmental health assessment products.

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Systematic Data Gathering

Primary information relevant to human hazard characterization generally comes from three data "streams":

1. Exposed humans
   - Occupational (adult males mostly)
   - Environmental (potentially all life-stages included)
   - Intentional (typically healthy young adult volunteers)
2. Exposed animals
   - Mammalian model systems (e.g. rodents, dogs, pigs, etc)
   - Non-mammalian model systems (e.g. frogs, zebrafish, etc)
   - Other animals (e.g. livestock, horses, cows, etc)
3. Cells/tissues exposed *in vitro*
   - Primary cells/tissue from species above
   - Immortalized neoplastic or non-neoplastic "normal" cell lines
   - Single-celled organisms

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Systematic Review in Literature Collection and Evaluation

Asking the right questions: using a PECO statement as a guide

- Population
- Exposure
- Comparator
- Outcomes

Steps in systematic review:

- Literature search
- Literature screening
- Literature evaluation

Use of graphics and tables to aid construction of a hazard characterization narrative

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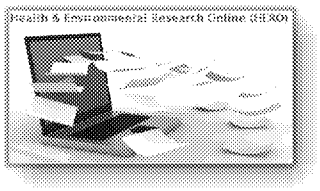
Development of the Supporting Literature Database

Health and Environmental Research Online (HERO)

- Database used to manage the scientific literature EPA identifies when developing environmental risk assessments for the public
  - https://hero.epa.gov/hero/
- Public can view references, including abstracts used to draft IRIS assessments
- Includes a search engine that searches various bibliographic databases



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In 2009, EPA released the HERO database, which is a database to manage scientific literature and increase transparency for programs like IRIS.
HERO is an "evergreen" database that is constantly updated and reflects the most recent research.
The public can access bibliographic information, including abstracts, for studies cited in IRIS assessments by clicking on links in the IRIS document which will bring them to www.epa.gov/hero or the public side of HERO.
Authorized HERO users, including authors, can access additional features through www.epa.gov/hero including the ability to:
Search several dozen bibliographic databases using a federated search engine. This is the LitSearch function of HERO that was shown earlier in the presentation.
Further, authorized users can access full-text of articles that have been imported into the HERO database.
Although the lit search process is executed in a different manner using HERO compared to the "old-fashioned" way, the end result and the fundamental process are basically the same:
Essentially HERO is a tool that helps EPA manage the lit search and peer review processes.

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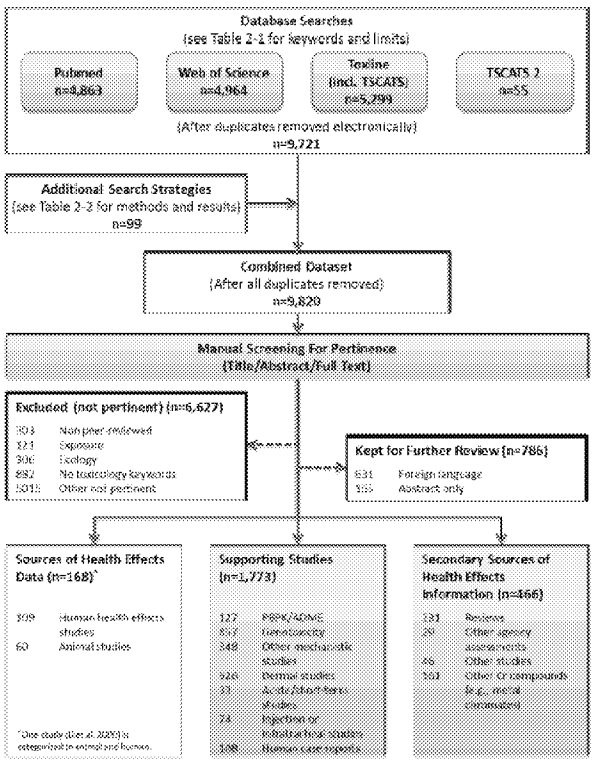
Initial Primary Literature Search and Review Materials

1. Literature search – PRISMA diagram
   - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
2. Evidence tables and graphics – study methods and results
3. Discussion of potential issues regarding study methods and quality
   - Start with all pertinent, publicly available studies
   - Exclude studies based on problem formulation
   - Possibly exclude studies with fundamental flaws

Literature Search Flow Diagram

- Lit. Search PRISMA Diagram
  - http://www.prisma-statement.org/
- Example: ethyl *tert* butyl ether (ETBE)
  - Literature organized in HERO
  - https://hero.epa.gov/hero/index.cfm/litflow/viewProject/project_id/1376



Sections of Preliminary Materials.....pic of literature flow diagram.

Example: Initial Screening Evaluation of Human Studies

	Cardiovascular	Dermal	Developmental	Endocrine/ Exocrine	Gastrointestinal	Hematological	Hepatic	Immunological	Musculoskeletal	Nasal	Neurological	Pulmonary	Renal	Reproductive	Ocular	Other effects[a]
Human studies – inhalation exposure																
Occupational Epidemiological Studies						1 0	1 0				1 1					
General Population Epidemiological Studies	1 1	2 0	5 2		1 0		1 0	9 7		2 0	2 0	4 2			2 1	2 2
Controlled Exposure Studies								1 0		7 6					5 4	2 2

Number of studies that examined the endpoint

Number of studies reporting ≥ 1 hazard(s) associated with exposure

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Effect or outcome categories are organized as columns, with different study designs or populations organized as different rows.

Example, continued – Animal

	Cardiovascular	Dermal	Developmental	Endocrine/ Exocrine	Gastrointestinal	Hematological	Hepatic	Immunological	Musculoskeletal	Nasal	Neurological	Pulmonary	Renal	Reproductive	Ocular	Other effects[a]
Animal studies - inhalation exposure																
Chronic	6	2		6	2	6	7	6	2	2	2	6	6	6	2	7
	0	0		1	0	0	5	0	0	0	0	1	2	3	0	4
Subchronic	3	1		3	3	3	6	3	2	3	4	3	7	3	3	7
	0	0		0	0	0	6	1	0	0	1	1	6	0	0	1
Short-term	9	4	1	8	6	7	17	9	6	9	18	13	16	10	7	23
	0	0	0	1	0	2	10	0	0	0	9	2	5	0	0	8
Acute										1	4	3			1	2
										1	4	3			1	2
Multigenerational			3				3						3	3		3
			1				2						2	1		1
Gestational	2		12	2			6	5			2	5	6	12		11
	0		10	0			4	3			0	0	3	3		4

Number of studies that examined the endpoint

Number of studies reporting ≥ 1 hazard(s) associated with exposure

Evidence Tables

Evidence Tables

- The “who, what, where, and when”
- Animal experimental
- Human epidemiological
- Mechanistic, if helpful

1 **3.4. Liver Effects**

2 **Table 3-3. Evidence pertaining to liver effects following oral or inhalation**
3 **exposure to hexavalent chromium**

Reference and study design	Results
Liver Weight – Oral	
NTP (2007) F344 Rat (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Percent change from control by exposure group for males: mg Cr VI/kg-d — Absolute liver weight — Relative liver weight 0 — -- — -- 1.7 — -5 — -3 3.5 — 5 — 3 5.9 — -3 — -3 11.2 — -16* — -11* 20.9 — -18* — -9* No statistically significant effects observed in females.
Chopra et al. (1998) Wistar Rat, Female (5-6/group) Water: 0, 25 ppm potassium dichromate; equivalent to 0, 1.4 mg Cr VI/kg-d 7 d/wk, 22 wk	Percent change from control by exposure group: mg Cr VI/kg-d — Relative liver weight 0 — -- 1.4 — 125*
Geetha et al. (2003) Sprague-Dawley Rat, Male (number/ group not reported) Gavage: 0, 30 mg Cr VI/kg-d given as potassium dichromate 7 d/wk, 30 d	Percent change from control by exposure group: mg Cr VI/kg-d — Relative liver weight 0 — -- 30 — 66.7*
Acharya et al. (2001) Wistar Rat, Male (5-6/group) Water: 0, 28 ppm potassium dichromate; equivalent to 0, 1.5 mg Cr VI/kg-d 7 d/wk, 22 wk	Percent change from control by exposure group: mg Cr VI/kg-d — Relative liver weight 0 — -- 1.5 — 125*
NTP (2007) B6C3F1 Mouse (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Absolute but not relative liver weight was statistically significantly decreased at the three highest doses in males and the two highest in females; this was attributed to a significant reduction in body weight.

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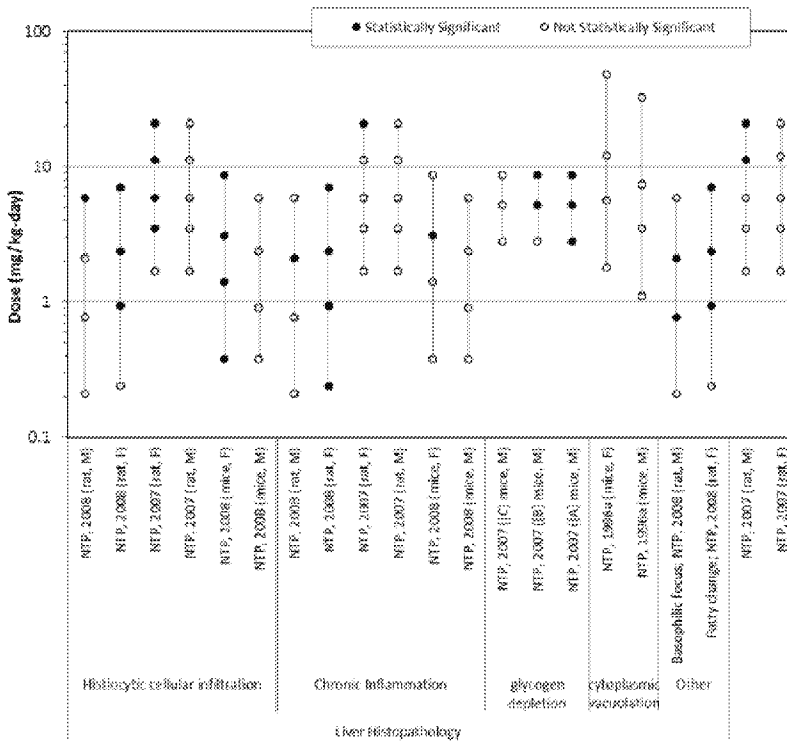
Evidence tables, organized by hazards.

Evidence Graphs

- Exposure-Response arrays of which concentrations were associated with statistically significant effects
- Generally, using author-reported statistical testing



Exposure response arrays

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Describe Support for the Association of Exposure with Toxicity

Toxicity

- What adverse effects are observed from the data collected?

Toxicokinetics

- What does the body do to the chemical?

Toxicodynamics and Mode of Action (MOA)

- What does the chemical do to the body…and how does the chemical act to produce a hazard?

Weight of evidence

- How likely is this chemical to cause non-cancer or cancer hazard, and under what conditions?

Causality Framework

- A way to organize and evaluate toxicity information to assess causality given those data.

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Mode of Action (MOA)

Mode of action:

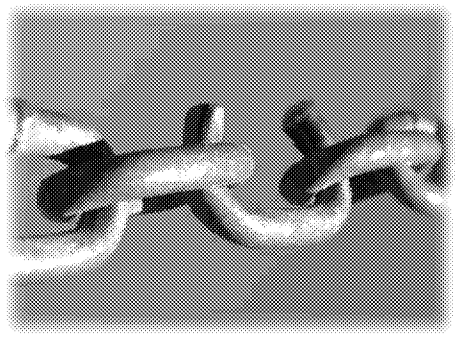
- The chain of biological "key" events leading to a hazard.

Key Events:

- Empirically observable precursor steps that are individually necessary elements or biomarkers.
- In combination, are sufficient for carcinogenesis.

Application:

- Identify active chemical species.
- Identify sensitive or susceptible subpopulations and lifestages.
- Contribute to integration of evidence "streams".
- Inform quantitative extrapolation.



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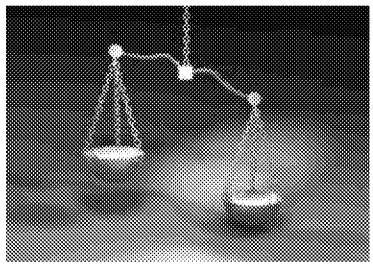
Although the default approaches for cancer and noncancer effects are linear and non-linear extrapolation in the low-dose region, respectively, EPA is now placing more consideration on mode of action (MOA) to inform the appropriate approach to extrapolation within the low-dose region. As a result, there are some noncancer health effects that have been determined to have a linear dose-response relationship and some cancer effects that have a nonlinear dose-response relationship.
The toxic mode of action is defined as a general description of the sequence of biological events leading to an adverse effect. The mode of action description is generally broken down into a series of "key events," which are empirically observable precursor steps that are themselves necessary elements of the mode of action, or they are biologically-based markers for such elements.

Systematic Weight-of-Evidence Evaluation (WOE)

Weight-of-Evidence:

- A system used for characterizing the extent to which the available data support the hypothesis that an agent causes cancer or non-cancer effects in humans.
- The approach outlined in EPA's guidelines for carcinogen risk assessment (2005):
  - considers all scientific information in determining whether and under what conditions an agent may cause cancer in humans, and
  - provides a narrative approach to characterize carcinogenicity rather than categories, and
  - uses pre-defined weight-of-evidence descriptors.



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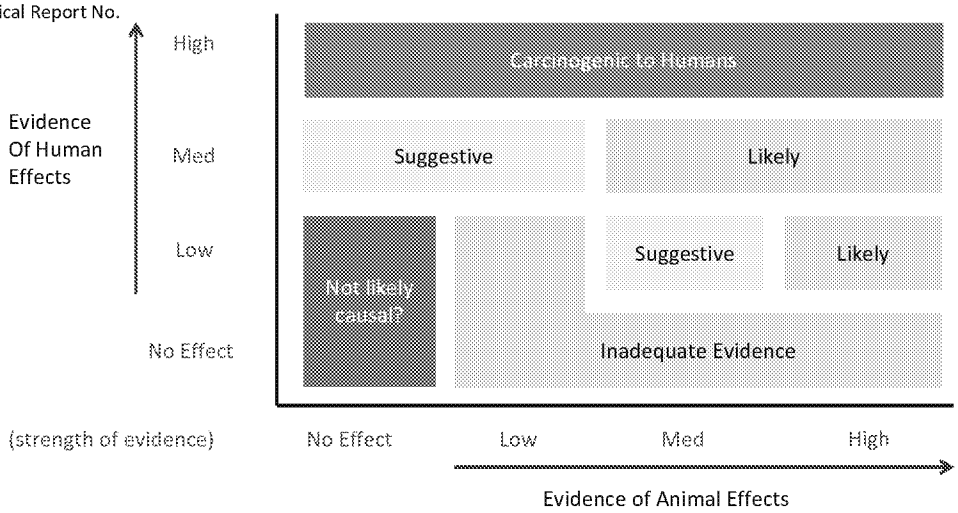
For Illustrative Purposes: Cancer WOE Integration

[Modified from International Agency for Research on Cancer (IARC), Technical Report No. 42, 2009.]



Evidence integration can be approached in a 2-step manner:

1. Determine strength of evidence individually for human and animal streams, considering mechanistic data
2. Determine overall weight of evidence conclusion regarding evidence for a human health effect

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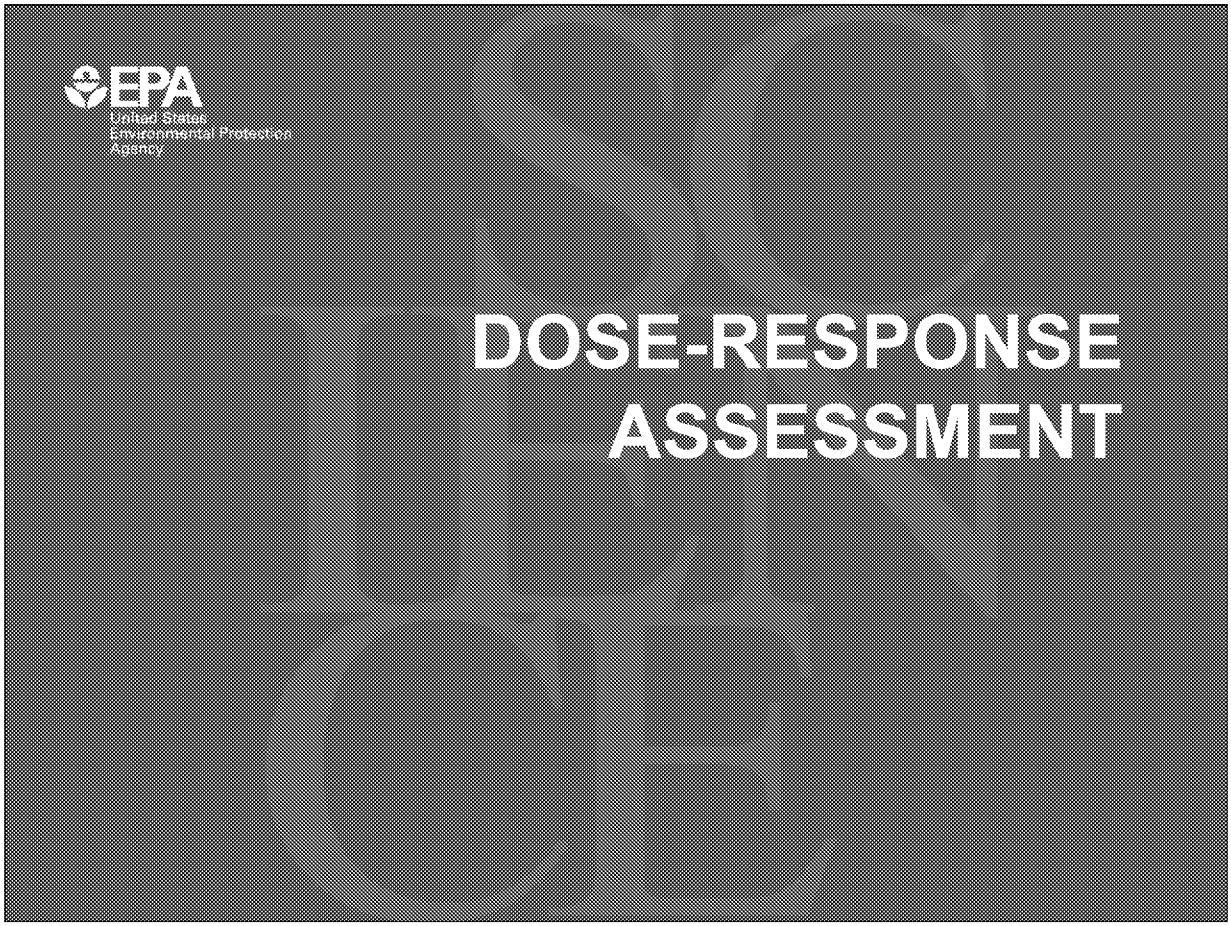
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DOSE-RESPONSE
ASSESSMENT

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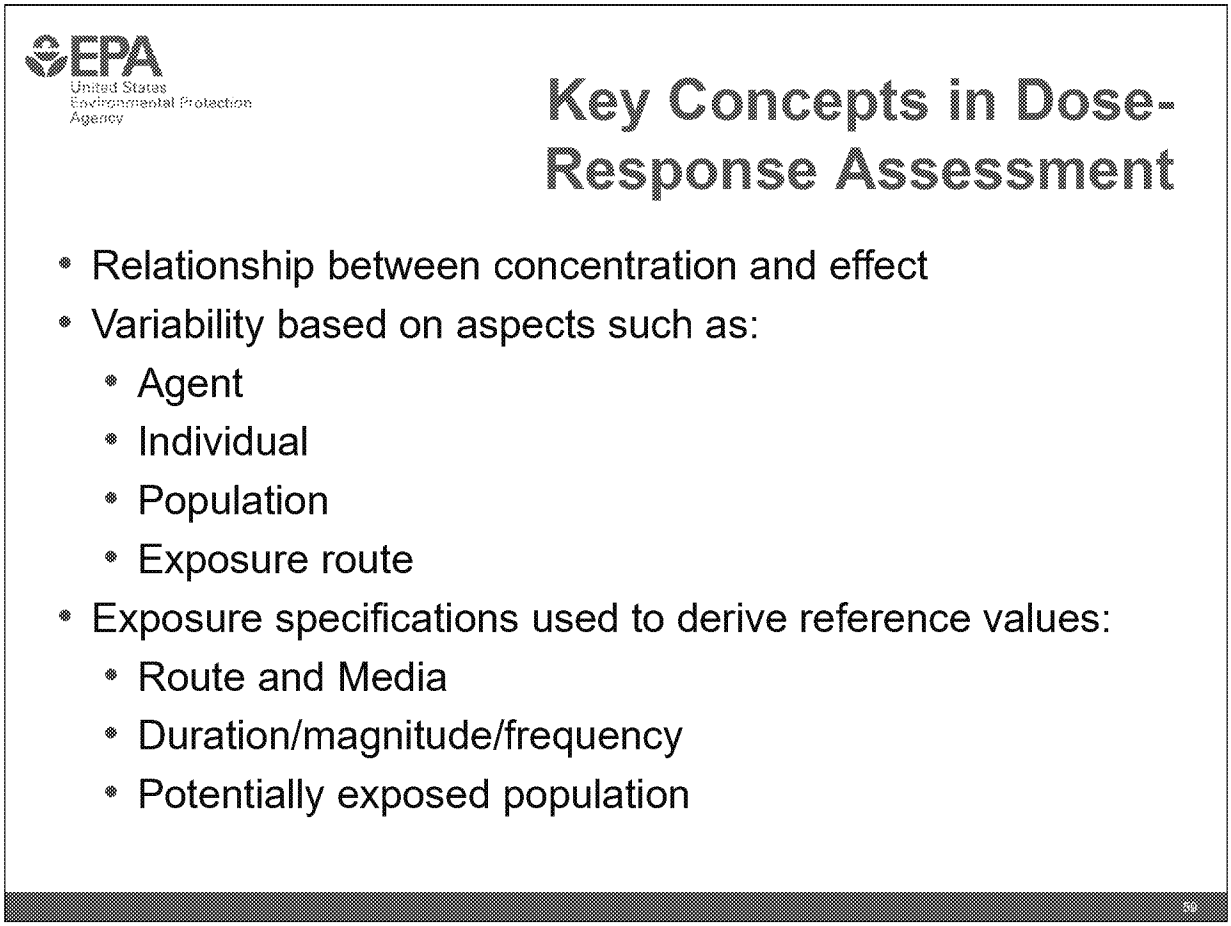
Elements of Dose-Response Assessment

1. Mode of action (MOA)
   - *(Described previously)*
2. Critical effect(s)
3. Point of Departure (POD)
4. Uncertainty Factors (UF)
   - *(only applied to noncancer outcomes)*



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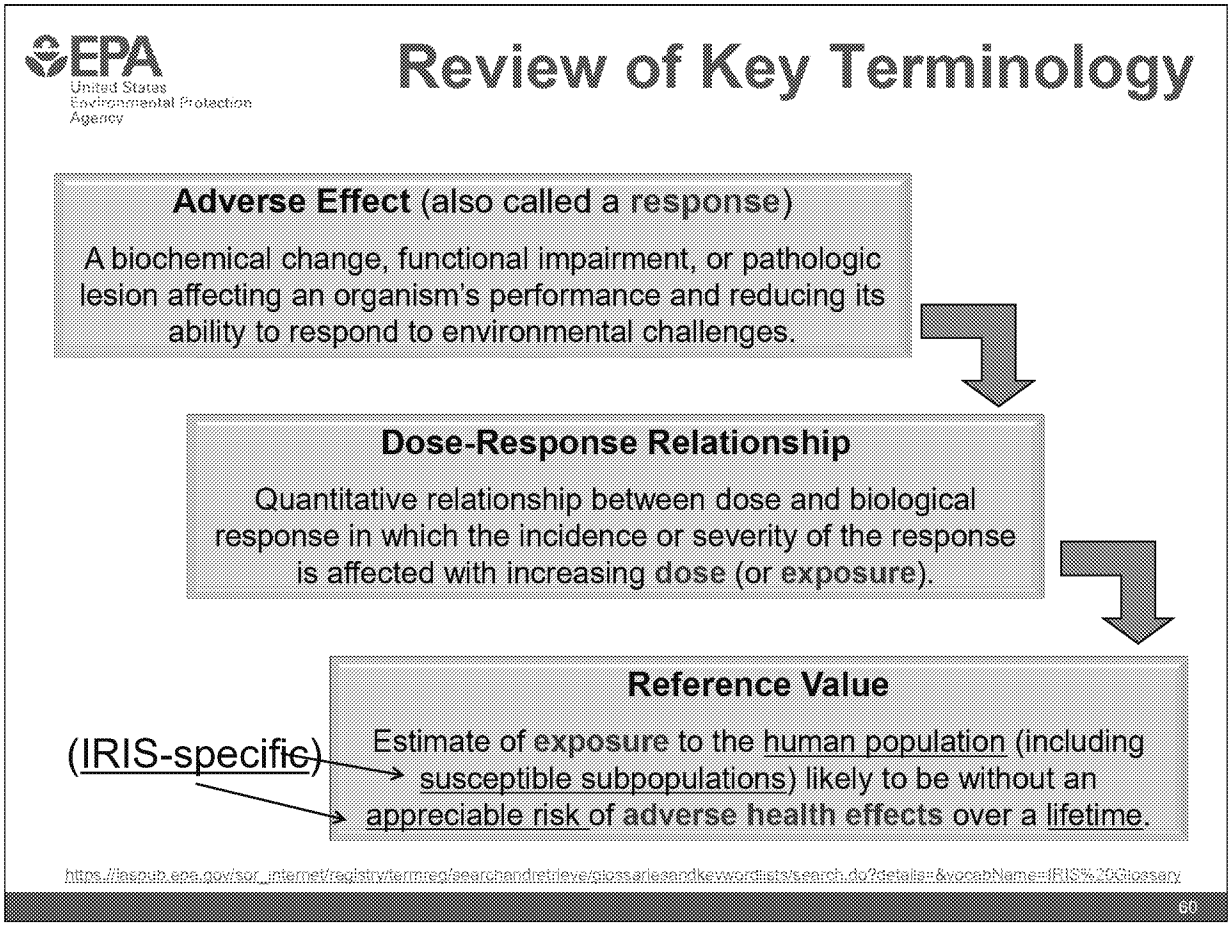
The primary focus of this course is on the dose- or concentration-response assessment component of the risk paradigm shown in this slide.
Typically, as the dose or concentration increases, the probability of an effect occurring or the severity of the effect increases. However, the dose or concentration at which effects begin to appear and the rate of increase of those effects within populations varies depending on the agent, the individual or population, the exposures route(s), and other factors.
Exposure specifications, as discussed in RAB 103, are integrated into the development of human health effect reference and risk values. As with any reference or risk value, the following exposure specifications must be considered in the determination of appropriate application of these values:
Exposure medium
Exposure route
Exposure duration, magnitude, and frequency
Potentially exposed population



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The key terms on this slide, covered in some of the previous courses, will appear frequently throughout the discussion of human health effect reference and risk values.
The first key term, "adverse effect," is also referred to in this course as a "response."
However, not all biological responses are adverse, but for the purpose of this course we use this term to refer to only those responses that are either adverse or are precursors to an adverse response in a chain of biological events.
In this course, we will be looking at the dose-response relationship for adverse or precursor effects in the low-dose region of the dose-response curve.
As defined in IRIS, which is the focus of this course, a reference value is: An estimate of an exposure for a given duration to the human population (including susceptible populations) that is likely to be without an appreciable risk of adverse health effects over a lifetime.
The key differences between the general definition provided in RAB 103 and the definition specific to IRIS are that:
IRIS values specify humans as the potentially exposed population (rather than the more general definition, which also encompasses ecological reference values),
susceptible populations are specifically protected by IRIS values,
the term "appreciable risk" is introduced in the IRIS definition, and
a lifetime exposure duration is specified in IRIS values.
Note how the definition of each of these terms ties into the next, demonstrating that the dose-response assessment is a process with many related components.

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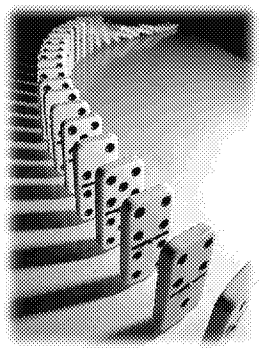
The Critical Effect

The Critical effect:

The adverse effect that occurs at the lowest dose, or its known precursor, that occurs to the most sensitive, relevant, species as the dose rate of an agent increases

Criteria for Critical Effect:

- Adverse or precursor to adverse
- Dose- or concentration-dependent
- Can occur in humans



If the critical effect is prevented, no other adverse effects are expected to occur

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A critical effect is defined in IRIS as the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases. In other words, if the critical effect is prevented from occurring, it is assumed that no other adverse effects will occur.
The risk assessor selects the critical effect from the available animal and human data.
The selected critical effect should meet the following criteria to be used for deriving a reference or risk value:
The effect should be
adverse or precursor to an adverse effect,
Dose-dependent in a manner that is significant at environmentally relevant concentrations, and
Biologically relevant to humans.

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Adverse Effect or Critical Effect?

- **Adverse effect:** A biochemical change, functional impairment, or pathologic lesion at any dose which affects an organism's performance and reduces its ability to respond to environmental challenges

- **Critical effect:** The adverse effect that occurs at the lowest dose, or its known precursor, which occurs to the most sensitive, relevant, species as the dose rate of an agent increases

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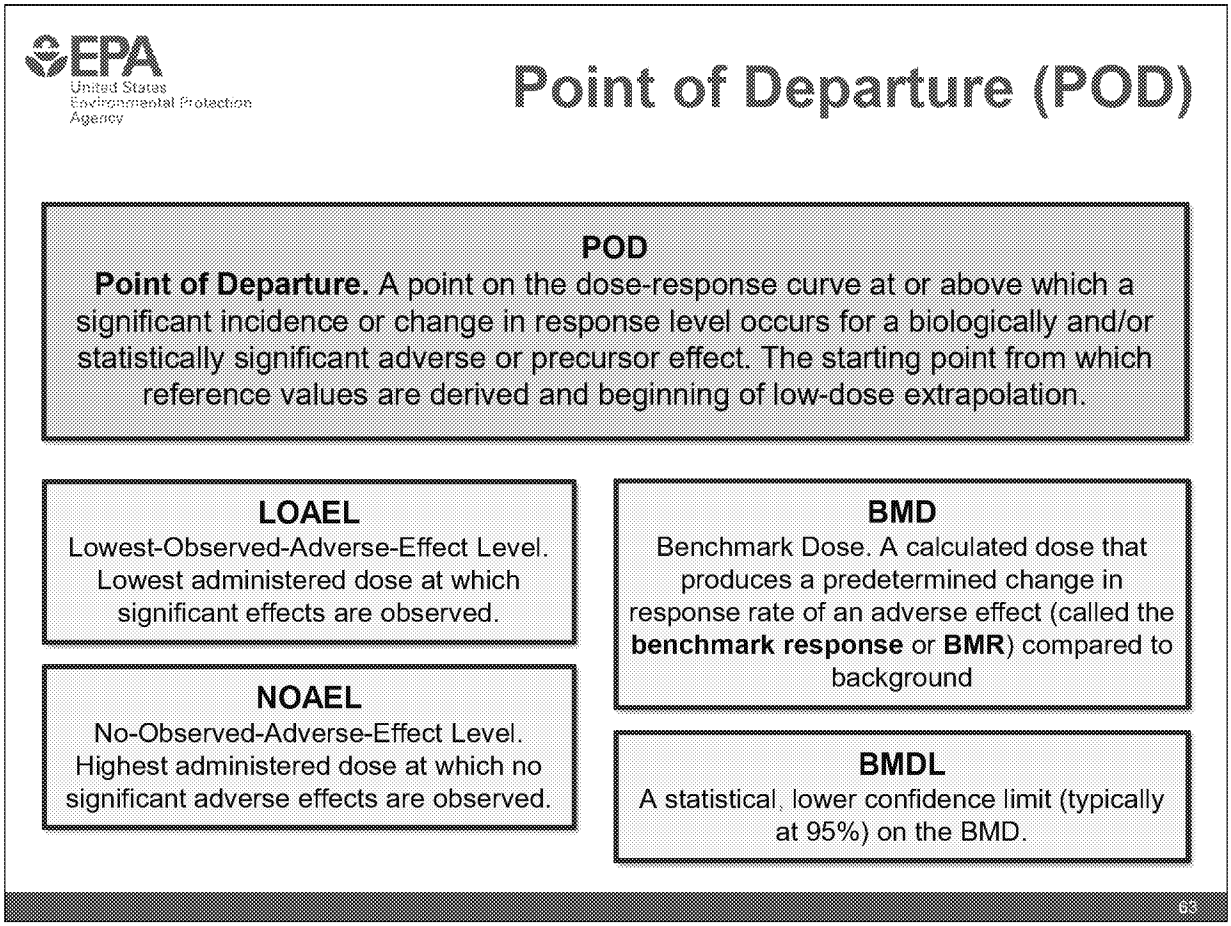

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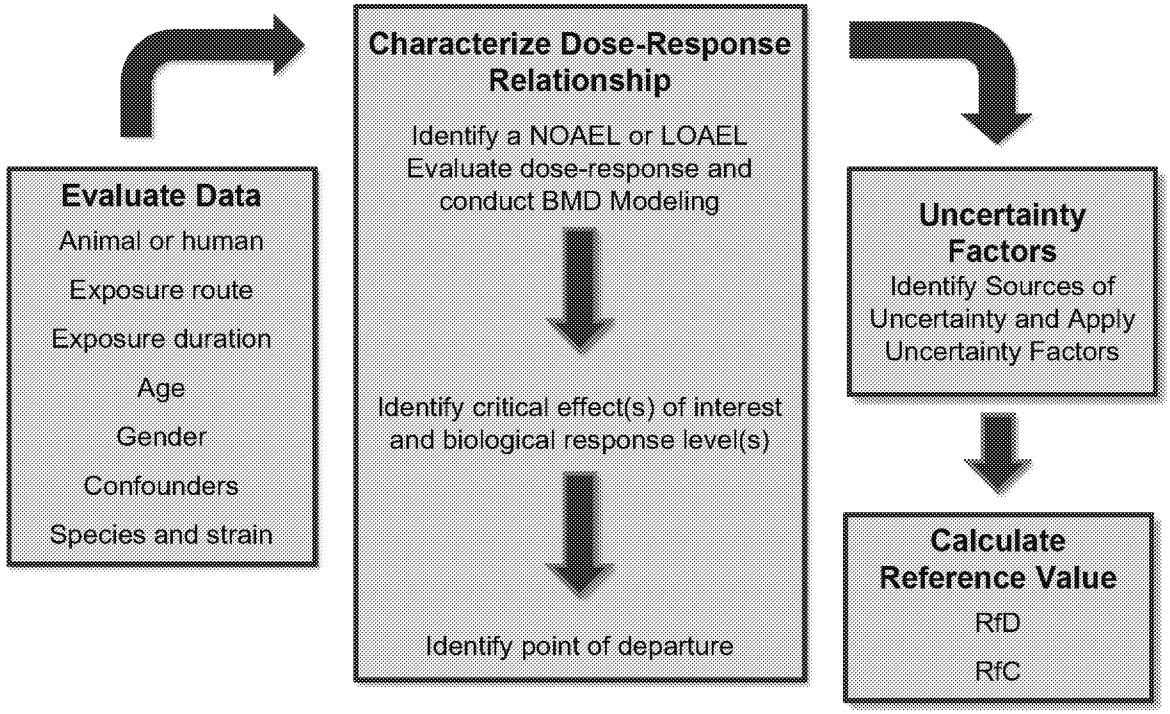
Discuss differences on when we use NOAEL/LOAEL and BMDL/BMD; LOAEL/NOAEL column are values based upon exposures used in specific studies, while the BMD/BMDL are calculated from study data to provide a response-specific dose level.

Dose-Response Assessment: Non-Cancer



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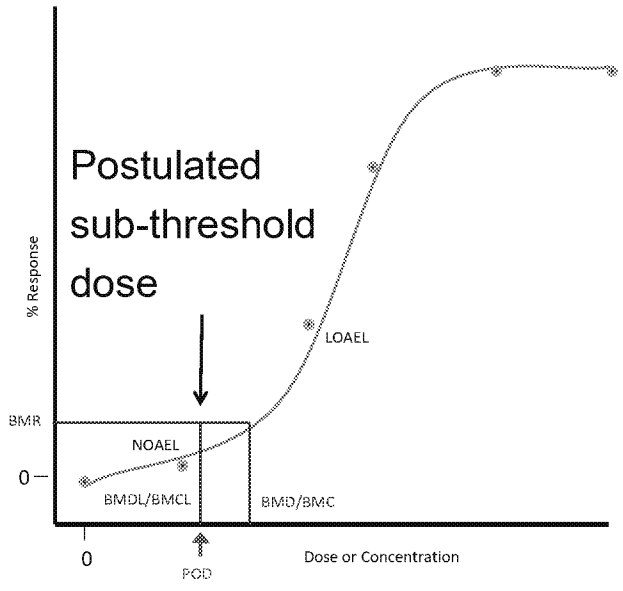
Major Assumptions in Noncancer Dose-response Assessment



Default approach: nonlinear dose-response relationship

Assumptions:

- A population threshold exists
- Reference values determined from POD represent sub-threshold doses
- Effects in animals will also occur in humans

Notable exceptions:

- PM, lead

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There are several major assumptions applied to the default approach for noncancer endpoints that contribute to scientific debate over using this approach. These include:
That a population threshold actually exists,
That a selected reference value represents doses below that threshold,
That preventing the critical effect protects against all other effects, and
That effects in animals will also occur in humans (many IRIS reference values are based on animal toxicological data).
More recent noncancer guidelines have abandoned the term threshold, noting the difficulty of empirically distinguishing dose-response relationships with true biologic thresholds from ones that are nonlinear at low doses.
There are now multiple toxicants (for example, PM and lead) for which low-dose linear concentration-response functions rather than thresholds have been derived for noncancer endpoints.
Noncancer risk assessments simply compare observed or predicted doses with the reference dose to yield a qualitative conclusion about the likelihood of harm.
The uncertainty in these assumptions is addressed through:
A thorough review of all data before the critical effect is selected, and
The application of uncertainty factors to increase confidence in the protectiveness of the reference values.

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Variability and Uncertainty

- **Variability**
  - Actual biological heterogeneity or diversity
- **Uncertainty**
  - A lack of knowledge regarding the extent of biological variability, or resulting from extrapolation: e.g. within populations, between species, across durations or concentrations.

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Use "what everyone ate for breakfast" as an illustration?
Some of the possible sources of uncertainties –

Human variability
Using animal data
Extrapolating the study duration
Extrapolating the exposure effect level
Relevance to target context (human exposures)
Strength of database
Quality of data
Risk characterization

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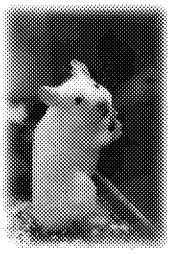
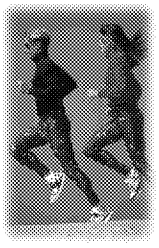
Uncertainty (and Variability) Factors

- UFH – Human variability
- UFA – Animal-to-human extrapolation
- UFS – Subchronic-to-chronic extrapolation
- UFL – LOAEL-to-NOAEL extrapolation
- UFD – Database deficiencies
- **UFC** – **Composite UF =** (UFH × UFA × UFS × UFL × UFD)





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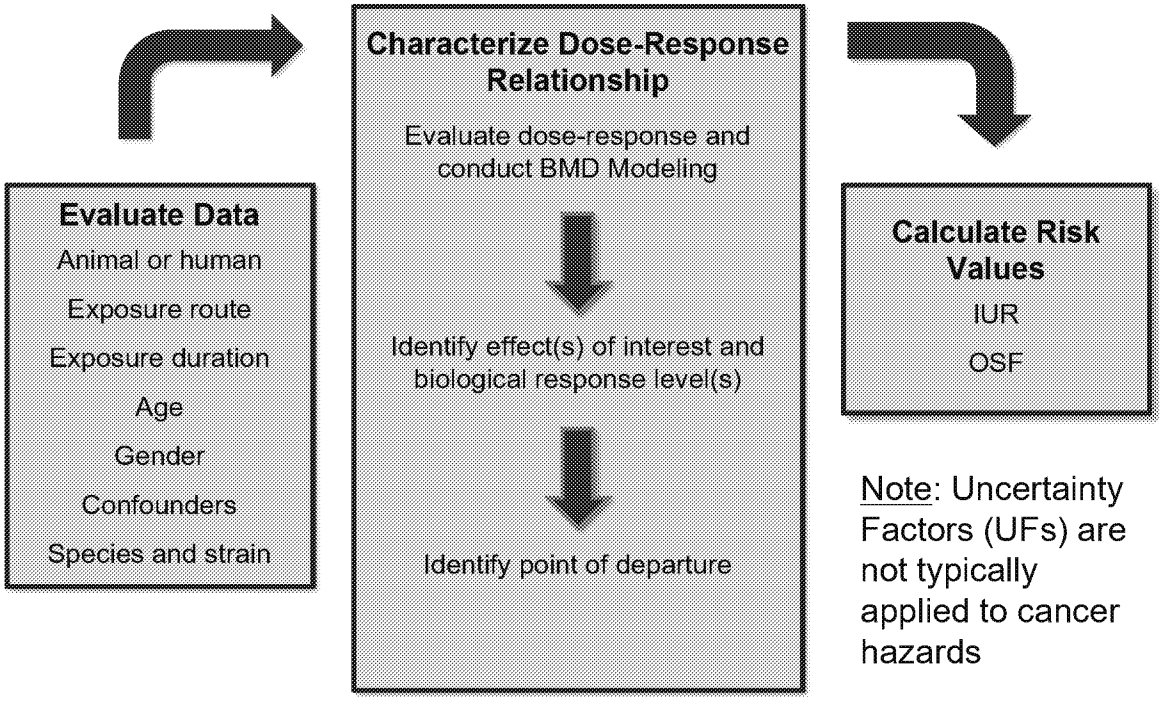
Noncancer References: Adjusting for Variability and Uncertainty

Reference Value = Dose ÷ Uncertainty

RfV = POD ÷ UFC

- RfV: An estimate of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

Dose-Response Assessment: Cancer



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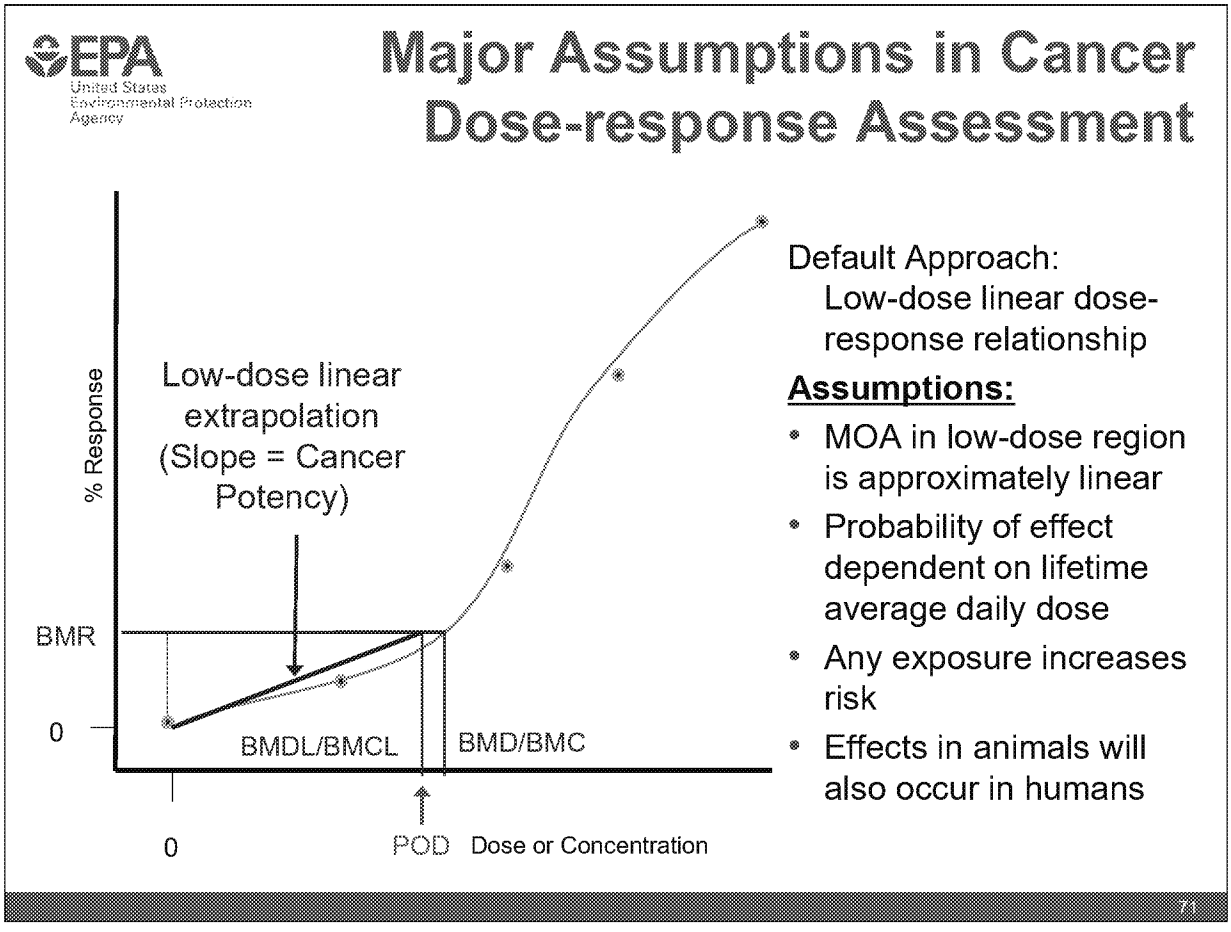
Cancer Toxicity Values

Inhalation Unit Risk (IUR):

- The upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a specified concentration
  - Typically 1 µg/m^3 in air

Oral cancer slope (OSF):

- An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime oral exposure to an agent



As with the default approach for noncancer assessments, there are several major assumptions applied to the default approach for cancer that contribute to scientific debate over using this approach. These include:
That the mode of action in the low-dose region is indeed linear;
That the probability of an effect occurring is dependent on the cumulative dose;
That any exposure can increase risk; and
That effects in animals will also occur in humans.

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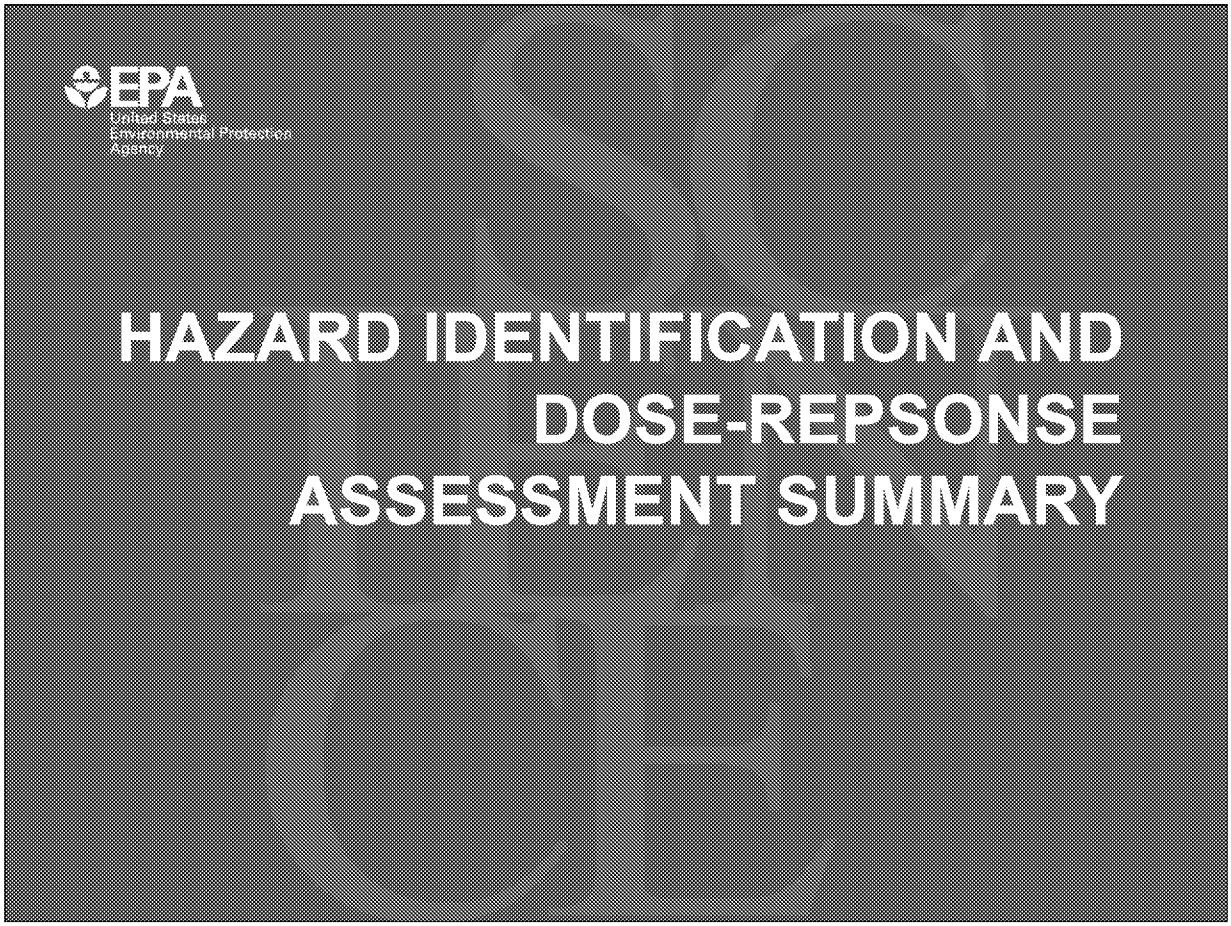
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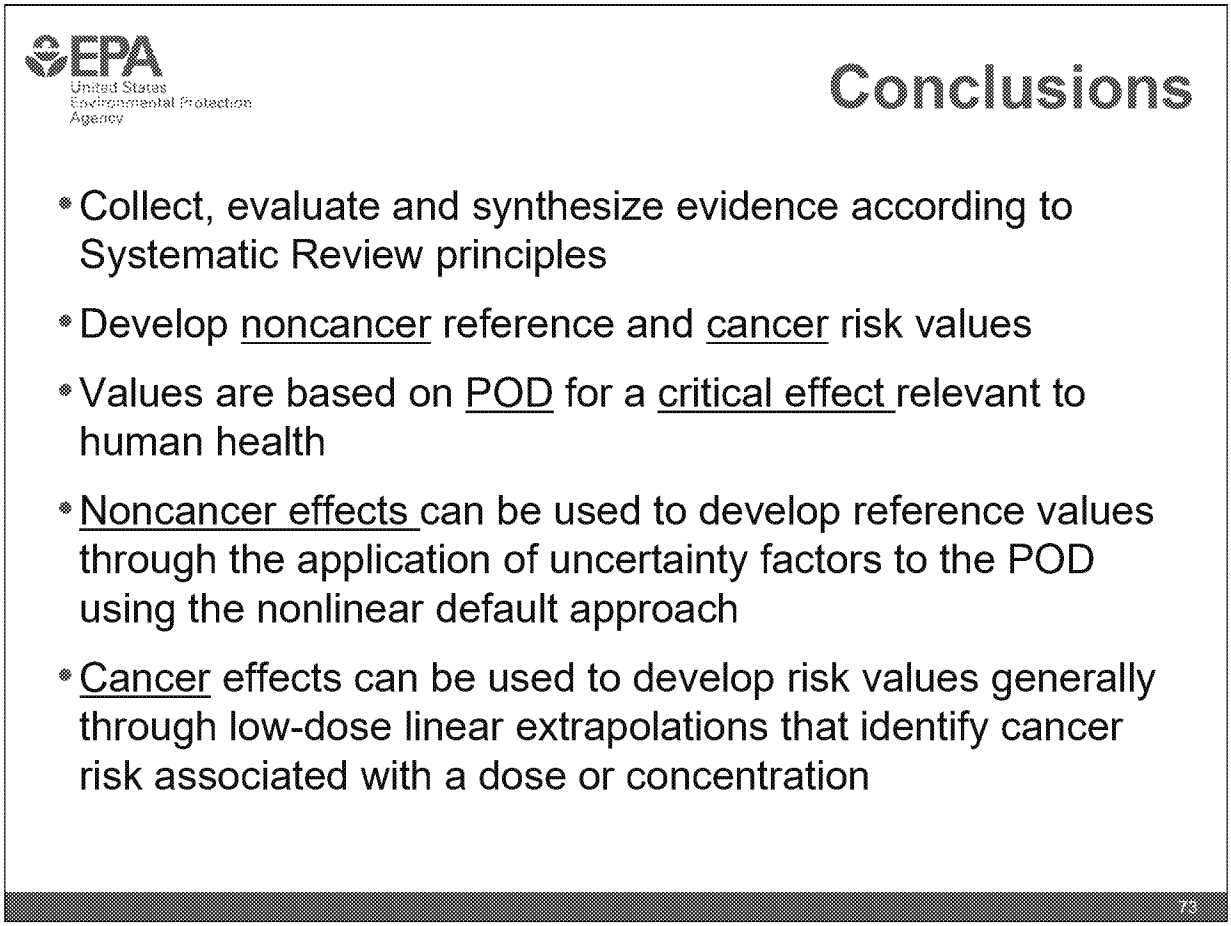
HAZARD IDENTIFICATION AND
DOSE-REPSONSE
ASSESSMENT SUMMARY



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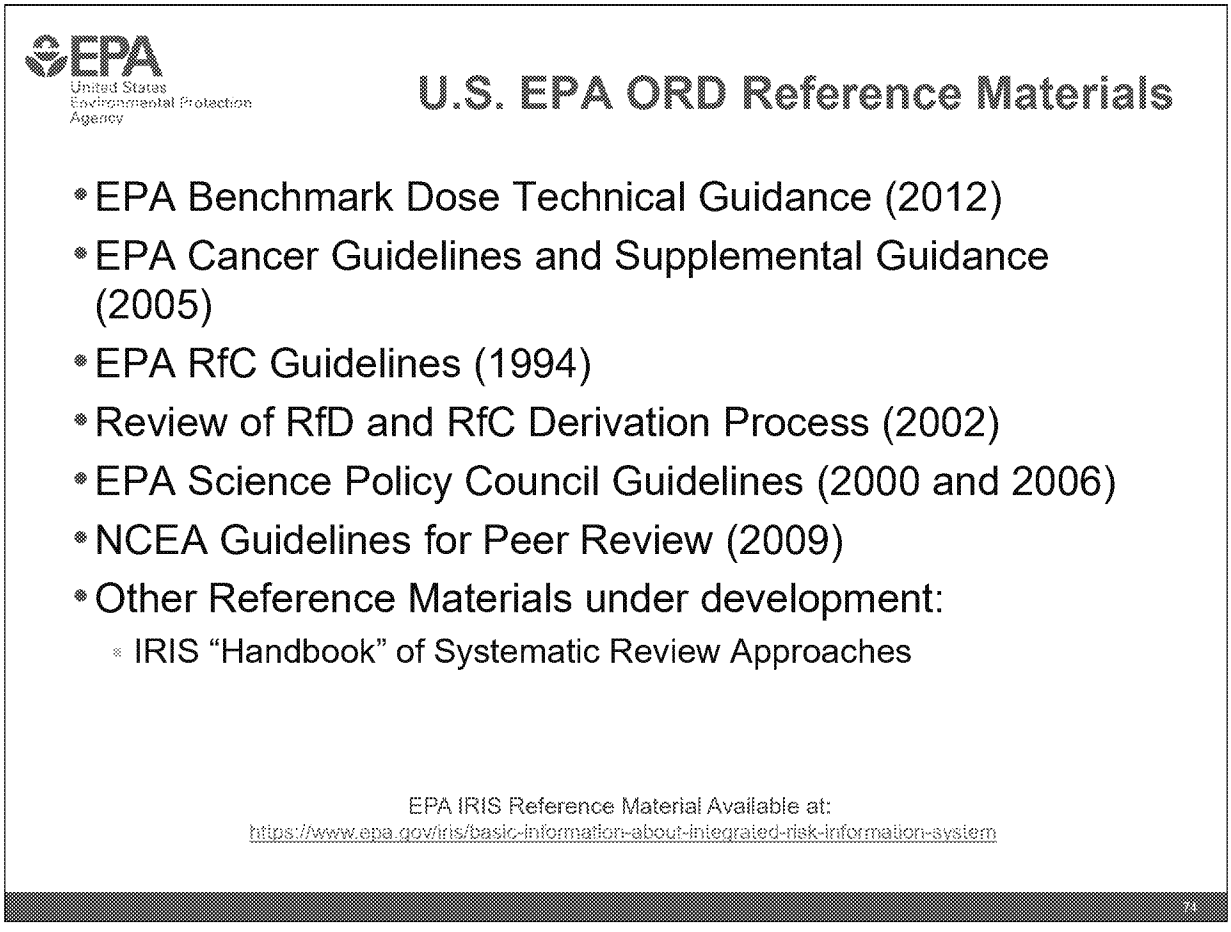
Note that these are general conclusions based upon evaluations using default approaches.
The type of reference and risk values that can be derived for a substance depend on the effect (whether cancer or noncancer).
Human health reference and risk values are based on a point of departure for a critical effect in the dose-response data.
Noncancer effects are can be used to develop human health effect reference values through the application of uncertainty factors to the point of departure using the default nonlinear approach
Cancer effects can be used to develop human health risk values generally through low-dose extrapolations that identify cancer risk associated with a dose or concentration.



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IRIS values and other pertinent substance-specific data are presented in many ways on the IRIS Website.
For risk assessors that are interested in using IRIS values instead of conducting a dose-response assessment of their own, these values and their supporting information are provided in detail in the IRIS toxicological review and summarized in two convenient resources on the IRIS Website: the IRIS Quickview and the IRIS Toxicological Review Summary.
It is important to note, however that full IRIS toxicological reviews are not available for most of the older substances on IRIS.
In addition, EPA provides general guidance for conducting cancer and noncancer risk assessments.
The guidance documents on this slide are posted on the IRIS Website.
These are applicable to the development and review of human health effect reference and risk values.